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(54) G-CSF analog compositions and methods

G-CSF Analoge und Verfahren zu ihrer Herstellung

Analogues de G-CSF et méthodes pour les obtenir

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Description

Field of the Invention

[0001] This invention relates to granulocyte colony stimulating factor ("G-CSF") analogs.

Background

[0002] Hematopoiesis is controlled by two systems: the cells within the bone marrow microenvironment and growth factors. The growth factors, also called colony stimulating factors, stimulate committed progenitor cells to proliferate and to form colonies of differentiating blood cells. One of these factors is granulocyte colony stimulating factor, herein called G-CSF, which preferentially stimulates the growth and development of neutrophils, indicating a potential use in neutropenic states. Welte et al., PNAS-USA 82: 1526-1530 (1985); Souza et al., Science 232: 61-65 (1986) and Gabrilove, J. Seminars in Hematology 26: (2) 1-14 (1989).

[0003] In humans, endogenous G-CSF is detectable in blood plasma. Jones et al., Bailliere's Clinical Hematology 2 (1): 83-111 (1989). G-CSF is produced by fibroblasts, macrophages, T cells trophoblasts, expression product of a single copy gene comprised of four exons and five introns located on chromosome seventeen. Transcription of this locus produces a mRNA species which is differentially processed, resulting in two forms of G-CSF mRNA, one version coding for a protein of 177 amino acids, the other coding for a protein of 174 amino acids, Nagata et al., EMBO J 5: 575-581 (1986), and the form comprised of 174 amino acids has been found to have the greatest specific in vivo biological activity. G-CSF is species cross-reactive, such that when human G-CSF is administered to another mammal such as a mouse, canine or monkey, sustained neutrophil leukocytosis is elicited. Moore et al., PNAS-USA 84: 7134-7138 (1987).

[0004] Human G-CSF can be obtained and purified from a number of sources. Natural human G-CSF (nhG-CSF) can be isolated from the supernatants of cultured human tumor cell lines. The development of recombinant DNA technology, see, for instance, U.S. Patent 4,810,643 (Souza) incorporated herein by reference, has enabled the production of commercial scale quantities of G-CSF in glycosylated form as a product of eukaryotic host cell expression, and of G-CSF in non-glycosylated form as a product of prokaryotic host cell expression.

[0005] G-CSF has been found to be useful in the treatment of indications where an increase in neutrophils will provide benefits. For example, for cancer patients, G-CSF is beneficial as a means of selectively stimulating neutrophil production to compensate for hematopoietic deficits resulting from chemotherapy or radiation therapy. Other indications include treatment of various infectious diseases and related conditions, such as sepsis, which is typically caused by a metabolite of bacteria. G-CSF is also useful alone, or in combination with other compounds, such as other cytokines, for growth or expansion of cells in culture, for example, for bone marrow transplants.

[0006] Signal transduction, the way in which G-CSF effects cellular metabolism, is not currently thoroughly understood. G-CSF binds to a cell-surface receptor which apparently initiates the changes within particular progenitor cells, leading to cell differentiation.

[0007] Various altered G-CSF's have been reported. Generally, for design of drugs, certain changes are known to have certain structural effects. For example, deleting one cysteine could result in the unfolding of a molecule which is, in its unaltered state, is normally folded via a disulfide bridge. There are other known methods for adding, deleting or substituting amino acids in order to change the function of a protein.

[0008] Recombinant human G-CSF mutants have been prepared, but the method of preparation does not include overall structure/function relationship information. For example, the mutation and biochemical modification of Cys 18 has been reported. Kuga et al., Biochem. Biophy. Res. Comm 159: 103-111 (1989); Lu et al., Arch. Biochem. Biophys. 268: 81-92 (1989).

[0009] In U.S. Patent No. 4, 810, 643, entitled, "Production of Pluripotent Granulocyte Colony-Stimulating Factor" (as cited above), polypeptide analogs and peptide fragments of G-CSF are disclosed generally. Specific G-CSF analogs disclosed include those with the cysteins at positions 17, 36, 42, 64, and 74 (of the 174 amino acid species or of those having 175 amino acids, the additional amino acid being an N-terminal methionine) substituted with another amino acid, (such as serine), and G-CSF with an alanine in the first (N-terminal) position.

[0010] EP 0 335 423 entitled "Modified human G-CSF" reportedly discloses the modification of at least one amino group in a polypeptide having hG-CSF activity.

[0011] EP 0 272 703 entitled "Novel Polypeptide" reportedly discloses G-CSF derivatives having an amino acid substituted or deleted at or "in the neighborhood" of the N terminus.

[0012] EP 0 459 630, entitled "Polypeptides" reportedly discloses derivatives of naturally occurring G-CSF having at least one of the biological properties of naturally occurring G-CSF and a solution stability of at least 35% at 5 mg/ml in which the derivative has at least Cys^{17} of the native sequence replaced by a Ser^{17} residue and Asp^{27} of the native sequence replaced by a Ser^{27} residue.

[0013] EP 0 256 843 entitled "Expression of G-CSF and Muteins Thereof and Their Uses" reportedly discloses a

modified DNA sequence encoding G-CSF wherein the N-terminus is modified for enhanced expression of protein in recombinant host cells, without changing the amino acid sequence of the protein.

[0014] EP 0 243 153 entitled "Human G-CSF Protein Expression" reportedly discloses G-CSF to be modified by inactivating at least one yeast KEX2 protease processing site for increased yield in recombinant production using yeast.

[0015] Shaw, U.S. Patent No. 4,904,584, entitled "Site-Specific Homogeneous Modification of Polypeptides," reportedly discloses lysine altered proteins.

[0016] WO/9012874 reportedly discloses cysteine altered variants of proteins.

[0017] Australian patent application Document No. AU-A-10948/92, entitled, "Improved Activation of Recombinant Proteins" reportedly discloses the addition of amino acids to either terminus of a G-CSF molecule for the purpose of aiding in the folding of the molecule after prokaryotic expression.

[0018] Australian patent application Document No. AU-A-76380/91, entitled, "Muteins of the Granulocyte Colony Stimulating Factor (G-CSF)" reportedly discloses muteins of the granulocyte stimulating factor G-CSF in the sequence Leu-Gly-His-Ser-Leu-Gly-Ile at position 50-56 of G-CSF with 174 amino acids, and position 53 to 59 of the G-CSF with 177 amino acids, or/and at least one of the four histadine residues at positions 43, 79, 156 and 170 of the mature G-CSF with 174 amino acids or at positions 46, 82, 159, or 173 of the mature G-CSF with 177 amino acids.

[0019] GB 2 213 821, entitled "Synthetic Human Granulocyte Colony Stimulating Factor Gene" reportedly discloses a synthetic G-CSF-encoding nucleic acid sequence incorporating restriction sites to facilitate the cassette mutagenesis of selected regions, and flanking restriction sites to facilitate the incorporation of the gene into a desired expression system.

[0020] G-CSF has reportedly been crystallized to some extent, e.g., EP 344 796, and the overall structure of G-CSF has been surmised, but only on a gross level. Bazan, Immunology Today 11: 350-354 (1990); Parry et al., J. Molecular Recognition 8: 107-110 (1988). To date, there have been no reports of the overall structure of G-CSF, and no systematic studies of the relationship of the overall structure and function of the molecule, studies which are essential to the systematic design of G-CSF analogs. Accordingly, there exists a need for a method of this systematic design of G-CSF analogs, and the resultant compositions.

Summary of the Invention

[0021] The three dimensional structure of G-CSF has now been determined to the atomic level. From this three-dimensional structure, one can now forecast with substantial certainty how changes in the composition of a G-CSF molecule may result in structural changes. These structural characteristics may be correlated with biological activity to design and produce G-CSF analogs.

[0022] Although others had speculated regarding the three dimensional structure of G-CSF, Bazan, Immunology Today 11: 350-354 (1990); Parry et al., J. Molecular Recognition 8: 107-110 (1988), these speculations were of no help to those wishing to prepare G-CSF analogs either because the surmised structure was incorrect (Parry et al., supra) and/or because the surmised structure provided no detail correlating the constituent moieties with structure. The present determination of the three-dimensional structure to the atomic level is by far the most complete analysis to date, and provides important information to those wishing to design and prepare G-CSF analogs. For example, from the present three dimensional structural analysis, precise areas of hydrophobicity and hydrophilicity have been determined.

[0023] Relative hydrophobicity is important because it directly relates to the stability of the molecule. Generally, biological molecules, found in aqueous environments, are externally hydrophilic and internally hydrophobic; in accordance with the second law of thermodynamics provides, this is the lowest energy state and provides for stability. Although one could have speculated that G-CSF's internal core would be hydrophobic, and the outer areas would be hydrophilic, one would have had no way of knowing specific hydrophobic or hydrophilic areas. With the presently provided knowledge of areas of hydrophobicity/philicity, one may forecast with substantial certainty which changes to the G-CSF molecule will affect the overall structure of the molecule.

[0024] As a general rule, one may use knowledge of the geography of the hydrophobic and hydrophilic regions to design analogs in which the overall G-CSF structure is not changed, but change does affect biological activity ("biological activity" being used here in its broadest sense to denote function). One may correlate biological activity to structure. If the structure is not changed, and the mutation has no effect on biological activity, then the mutation has no biological function. If, however, the structure is not changed and the mutation does affect biological activity, then the residue (or atom) is essential to at least one biological function. Some of the present working examples were designed to provide no change in overall structure, yet have a change in biological function.

[0025] Based on the correlation of structur to biological activity, the present invention relates to G-CSF analogs. These analogs are molecules which have more, fewer, different or modified amino acid residues from the G-CSF amino acid sequence. The modifications may be by addition, substitution, or deletion of one or more amino acid residues. The modification may include the addition or substitution of analogs of the amino acids themselves, such as peptidomimetics or amino acids with altered moieties such as altered side groups. The G-CSF used as a basis for comparison may

be of human, animal or recombinant nucleic acid-technology origin (although the working examples disclosed herein are based on the recombinant production of the 174 amino acid species of human G-CSF, having an extra N-terminus methionyl residue). The analogs may possess functions different from natural human G-CSF molecule, or may exhibit the same functions, or varying degrees of the same functions. For example, the analogs may be designed to have a higher or lower biological activity, have a longer shelf-life or a decrease in stability, be easier to formulate, or more difficult to combine with other ingredients. The analogs may have no hematopoietic activity, and may therefore be useful as an antagonist against G-CSF effect (as, for example, in the overproduction of G-CSF). From time to time herein the present analogs are referred to as proteins or peptides for convenience, but contemplated herein are other types of molecules, such as peptidomimetics or chemically modified peptides.

[0026] In another aspect, the present disclosure relates to related compositions containing a G-CSF analog as an active ingredient. The term, "related composition," as used herein, is meant to denote a composition which may be obtained once the identity of the G-CSF analog is ascertained (such as a G-CSF analog labeled with a detectable label, related receptor or pharmaceutical composition). Also considered a related composition are chemically modified versions of the G-CSF analog, such as those having attached at least one polyethylene glycol molecule.

[0027] For example, one may prepare a G-CSF analog to which a detectable label is attached, such as a fluorescent, chemiluminescent or radioactive molecule.

[0028] Another example is a pharmaceutical composition which may be formulated by known techniques using known materials, see, e.g., Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, Pennsylvania 18042) pages 1435-1712, which are herein incorporated by reference. Generally, the formulation will depend on a variety of factors such as administration, stability, production concerns and other factors. The G-CSF analog may be administered by injection or by pulmonary administration via inhalation. Enteric dosage forms may also be available for the present G-CSF analog compositions, and therefore oral administration may be effective. G-CSF analogs may be inserted into liposomes or other microcarriers for delivery, and may be formulated in gels or other compositions for sustained release. Although preferred compositions will vary depending on the use to which the composition will be put, generally, for G-CSF analogs having at least one of the biological activities of natural G-CSF, preferred pharmaceutical compositions are those prepared for subcutaneous injection or for pulmonary administration via inhalation, although the particular formulations for each type of administration will depend on the characteristics of the analog.

[0029] Another example of related composition is a receptor for the present analog. As used herein, the term "receptor" indicates a moiety which selectively binds to the present analog molecule. For example, antibodies, or fragments thereof, or "recombinant antibodies" (see Huse et al., Science 246:1275 (1989)) may be used as receptors. Selective binding does not mean only specific binding (although binding-specific receptors are encompassed herein), but rather that the binding is not a random event. Receptors may be on the cell surface or intra- or extra-cellular, and may act to effectuate, inhibit or localize the biological activity of the present analogs. Receptor binding may also be a triggering mechanism for a cascade of activity indirectly related to the analog itself. Also contemplated herein are nucleic acids, vectors containing such nucleic acids and host cells containing such nucleic acids which encode such receptors.

[0030] Another example of a related composition is a G-CSF analog with a chemical moiety attached. Generally, chemical modification may alter biological activity or antigenicity of a protein, or may alter other characteristics, and these factors will be taken into account by a skilled practitioner. As noted above, one example of such chemical moiety is polyethylene glycol. Modification may include the addition of one or more hydrophilic or hydrophobic polymer molecules, fatty acid molecules, or polysaccharide molecules. Examples of chemical modifiers include polyethylene glycol, alkl|polyethylene glycols, Dl-poly(amino acids), polyvinylpyrrolidone, polyvinyl alcohol, pyran copolymer, acetic acid/acylation, proprionic acid, palmitic acid, stearic acid, dextran, carboxymethyl cellulose, pullulan, or agarose. See, Francis, *Focus on Growth Factors* 3: 4-10 (May 1992) (published by Mediscript, Mountview Court, Friern Barnet Lane, London N20 OLD, UK). Also, chemical modification may include an additional protein or portion thereof, use of a cytotoxic agent, or an antibody. The chemical modification may also include lecithin.

[0031] In another aspect, the present disclosure relates to nucleic acids encoding such analogs. The nucleic acids may be DNAs or RNAs or derivatives thereof, and will typically be cloned and expressed on a vector, such as a phage or plasmid containing appropriate regulatory sequences. The nucleic acids may be labeled (such as using a radioactive, chemiluminescent, or fluorescent label) for diagnostic or prognostic purposes, for example. The nucleic acid sequence may be optimized for expression, such as including codons preferred for bacterial expression. The nucleic acid and its complementary strand, and modifications thereof which do not prevent encoooding of the desired analog are here contemplated.

[0032] In another aspect, the present disclosure relates to host cells containing the above nucleic acids encoding the present analogs. Host cells may be eukaryotic or prokaryotic, and expression systems may include extra steps relating to the attachment (or prevention) of sugar groups (glycosylation), proper folding of the molecule, the addition or deletion of leader sequences or other factors incident to recombinant expression.

[0033] In another aspect the present disclosure relates to antisense nucleic acids which act to prevent or modify the

type or amount of expression of such nucleic acid sequences. These may be prepared by known methods.

[0034] In another aspect of the present disclosure, the nucleic acids encoding a present analog may be used for gene therapy purposes, for example, by placing a vector containing the analog-encoding sequence into a recipient so the nucleic acid itself is expressed inside the recipient who is in need of the analog composition. The vector may first be placed in a carrier, such as a cell, and then the carrier placed into the recipient. Such expression may be localized or systemic. Other carriers include non-naturally occurring carriers, such as liposomes or other microcarriers or particles, which may act to mediate gene transfer into a recipient.

[0035] The present disclosure also provides for computer programs for the expression (such as visual display) of the G-CSF or analog three dimensional structure, and further, a computer program which expresses the identity of each constituent of a G-CSF molecule and the precise location within the overall structure of that constituent, down to the atomic level. Set forth below is one example of such program. There are many currently available computer programs for the expression of the three dimensional structure of a molecule. Generally, these programs provide for inputting of the coordinates for the three dimensional structure of a molecule (i.e., for example, a numerical assignment for each atom of a G-CSF molecule along an x, y, and z axis), means to express (such as visually display) such coordinates, means to alter such coordinates and means to express an image of a molecule having such altered coordinates. One may program crystallographic information, i.e., the coordinates of the location of the atoms of a G-CSF molecule in three dimension space, wherein such coordinates have been obtained from crystallographic analysis of said G-CSF molecule, into such programs to generate a computer program for the expression (such as visual display) of the G-CSF three dimensional structure. Also provided, therefore, is a computer program for the expression of G-CSF analog three dimensional structure. Preferred is the computer program Insight II, version 4, available from Biosym, San Diego, California, with the coordinates as set forth in FIGURE 5 input. Preferred expression means is on a Silicon Graphics 320 VGX computer, with Crystal Eyes glasses (also available from Silicon Graphics), which allows one to view the G-CSF molecule or its analog stereoscopically. Alternatively, the present G-CSF crystallographic coordinates and diffraction data are also deposited in the Protein Data Bank, Chemistry Department, Brookhaven National Laboratory, Upton, New York 119723, USA. One may use these data in preparing a different computer program for expression of the three dimensional structure of a G-CSF molecule or analog thereof. Therefore, another aspect of the present invention is a computer program for the expression of the three dimensional structure of a G-CSF molecule. Also provided is said computer program for visual display of the three dimensional structure of a G-CSF molecule; and further, said program having means for altering such visual display. Apparatus useful for expression of such computer program, particularly for the visual display of the computer image of said three dimensional structure of a G-CSF molecule or analog thereof is also therefore here provided, as well as means for preparing said computer program and apparatus.

[0036] The computer program is useful for preparation of G-CSF analogs because one may select specific sites on the G-CSF molecule for alteration and readily ascertain the effect the alteration will have on the overall structure of the G-CSF molecule. Selection of said site for alteration will depend on the desired biological characteristic of the G-CSF analog. If one were to randomly change said G-CSF molecule (r-met-hu-G-CSF) there would be 175^{20} possible substitutions, and even more analogs having multiple changes, additions or deletions. By viewing the three dimensional structure wherein said structure is correlated with the composition of the molecule, the selection for sites of alteration is no longer a random event, but sites for alteration may be determined rationally.

[0037] As set forth above, identity of the three dimensional structure of G-CSF, including the placement of each constituent down to the atomic level has now yielded information regarding which moieties are necessary to maintain the overall structure of the G-CSF molecule. One may therefore select whether to maintain the overall structure of the G-CSF molecule when preparing a G-CSF analog of the present invention, or whether (and how) to change the overall structure of the G-CSF molecule when preparing a G-CSF analog of the present invention. Optionally, once one has prepared such analog, one may test such analog for a desired characteristic.

[0038] One may, for example, seek to maintain the overall structure possessed by a non-altered natural or recombinant G-CSF molecule. The overall structure is presented in Figures 2, 3, and 4, and is described in more detail below. Maintenance of the overall structure may ensure receptor binding, a necessary characteristic for an analog possessing the hematopoietic capabilities of natural G-CSF (if no receptor binding, signal transduction does not result from the presence of the analog). It is contemplated that one class of G-CSF analogs will possess the three dimensional core structure of a natural or recombinant (non-altered) G-CSF molecule, yet possess different characteristics, such as an increased ability to selectively stimulate neutrophils. Another class of G-CSF analogs are those with a different overall structure which diminishes the ability of a G-CSF analog molecule to bind to a G-CSF receptor, and possesses a diminished ability to selectively stimulate neutrophils as compared to non-altered natural or recombinant G-CSF.

[0039] For example, it is now known which moieties within the internal regions of the G-CSF molecule are hydrophobic, and, correspondingly, which moieties on the external portion of the G-CSF molecule are hydrophilic. Without knowledge of the overall three dimensional structure, preferably to the atomic level as provided herein, one could not forecast which alterations within this hydrophobic internal area would result in a change in the overall structural conformation of the molecule. An overall structural change could result in a functional change, such as lack of receptor bind-

ing, for example, and therefore, diminishment of biological activity as found in non-altered G-CSF. Another class of G-CSF analogs is therefore G-CSF analogs which possess the same hydrophobicity as (non-altered) natural or recombinant G-CSF. More particularly, another class of G-CSF analogs possesses the same hydrophobic moieties within the four helical bundle of its internal core as those hydrophobic moieties possessed by (non-altered) natural or recombinant G-CSF yet have a composition different from said non-altered natural or recombinant G-CSF.

[0040] Another example relates to external loops which are structures which connect the internal core (helices) of the G-CSF molecule. From the three dimensional structure -- including information regarding the spatial location of the amino acid residues -- one may forecast that certain changes in certain loops will not result in overall conformational changes. Therefore, another class of G-CSF analogs provided herein is that having an altered external loop but possessing the same overall structure as (non-altered) natural or recombinant G-CSF. More particularly, another class of G-CSF analogs provided herein are those having an altered external loop, said loop being selected from the loop present between helices A and B; between helices B and C; between helices C and D; between helices D and A, as those loops and helices are identified herein. More particularly, said loops, preferably the AB loop and/or the CD loop are altered to increase the half life of the molecule by stabilizing said loops. Such stabilization may be by connecting all or a portion of said loop(s) to a portion of an alpha helical bundle found in the core of a G-CSF (or analog) molecule. Such connection may be via beta sheet, salt bridge, disulfide bonds, hydrophobic interaction or other connecting means available to those skilled in the art, wherein such connecting means serves to stabilize said external loop or loops. For example, one may stabilize the AB or CD loops by connecting the AB loop to one of the helices within the internal region of the molecule.

[0041] The N-terminus also may be altered without change in the overall structure of a G-CSF molecule, because the N-terminus does not effect structural stability of the internal helices, and, although the external loops are preferred for modification, the same general statements apply to the N-terminus.

[0042] Additionally, such external loops may be the site(s) for chemical modification because in (non-altered) natural or recombinant G-CSF such loops are relatively flexible and tend not to interfere with receptor binding. Thus, there would be additional room for a chemical moiety to be directly attached (or indirectly attached via another chemical moiety which serves as a chemical connecting means). The chemical moiety may be selected from a variety of moieties available for modification of one or more function of a G-CSF molecule. For example, an external loop may provide sites for the addition of one or more polymer which serves to increase serum half-life, such as a polyethylene glycol molecule. Such polyethylene glycol molecule(s) may be added wherein said loop is altered to include additional lysines which have reactive side groups to which polyethylene glycol moieties are capable of attaching. Other classes of chemical moieties may also be attached to one or more external loops, including but not limited to other biologically active molecules, such as receptors, other therapeutic proteins (such as other hematopoietic factors which would engender a hybrid molecule), or cytotoxic agents (such as diphtheria toxin). This list is of course not complete; one skilled in the art possessed of the desired chemical moiety will have the means to effect attachment of said desired moiety to the desired external loop. Therefore, another class of the present G-CSF analogs includes those with at least one alteration in an external loop wherein said alteration provides for the addition of a chemical moiety such as at least one polyethylene glycol molecule.

[0043] Deletions, such as deletions of sites recognized by proteins for degradation of the molecule, may also be effectual in the external loops. This provides alternative means for increasing half-life of a molecule otherwise having the G-CSF receptor binding and signal transduction capabilities (i.e., the ability to selectively stimulate the maturation of neutrophils). Therefore, another class of the present G-CSF analogs includes those with at least one alteration in an external loop wherein said alteration decreases the turnover of said analog by proteases. Preferred loops for such alterations are the AB loop and the CD loop. One may prepare an abbreviated G-CSF molecule by deleting a portion of the amino acid residues found in the external loops (identified in more detail below), said abbreviated G-CSF molecule may have additional advantages in preparation or in biological function.

[0044] Another example relates to the relative charges between amino acid residues which are in proximity to each other. As noted above, the G-CSF molecule contains a relatively tightly packed four helical bundle. Some of the faces on the helices face other helices. At the point (such as a residue) where a helix faces another helix, the two amino acid moieties which face each other may have the same charge, and thus tend to repel each other, which lends instability to the overall molecule. This may be eliminated by changing the charge (to an opposite charge or a neutral charge) of one or both of the amino acid moieties so that there is no repelling. Therefore, another class of G-CSF analogs includes those G-CSF analogs having been altered to modify instability due to surface interactions, such as electron charge location.

[0045] The present invention relates to methods for designing G-CSF analogs and related compositions and the products of those methods. The end products of the methods may be the G-CSF analogs as defined above or related compositions. For instance, the examples disclosed herein demonstrate (a) the effects of changes in the constituents (i.e., chemical moieties) of the G-CSF molecule on the G-CSF structure and (b) the effects of changes in structure on biological function. Essentially, therefore, an aspect of the present invention is a method for preparing a G-CSF analog

comprising the steps of:

(a) viewing at an amino acid or atomic level information conveying the three dimensional structure of a G-CSF molecule as set forth in Figure 5 wherein the chemical moieties, such as each amino acid residue or each atom of each amino acid residue, of the G-CSF molecule are correlated with said structure;
(b) selecting from said information a site on a G-CSF molecule for alteration;
(c) preparing a G-CSF analog molecule having such alteration; and
(d) optionally, testing such G-CSF analog molecule for a desired characteristic.

[0046] One may use the here provided computer programs for a computer-based method for preparing a G-CSF analog. Another aspect of the present invention is therefore a method for preparing a G-CSF analog according to the method of the preceeding paragraph based on the use of a computer comprising the steps of:

(a) providing computer expression of the three dimensional structure of a G-CSF molecule wherein the chemical moieties, such as each amino acid residue or each atom of each amino acid residue, of the G-CSF molecule are correlated with said structure;
(b) selecting from said computer expression a site on a G-CSF molecule for alteration;
(c) preparing a G-CSF molecule having such alteration; and
(d) optionally, testing such G-CSF molecule for a desired characteristic.

[0047] More specifically, the present invention provides a method for preparing a G-CSF analog comprising the steps of:

(a) viewing at the amino acid or atomic level the three dimensional structure of a G-CSF molecule as set forth in Figure 5 via a computer, said computer programmed (i) to express the coordinates of a G-CSF molecule in three dimensional space, and (ii) to allow for entry of information for alteration of said G-CSF expression and viewing thereof;
(b) selecting a site on said visual image of said G-CSF molecule for alteration;
(c) entering information for said alteration on said computer;
(d) viewing a three dimensional structure of said altered G-CSF molecule via said computer;
(e) optionally repeating steps (a)-(e);
(f) preparing a G-CSF analog with said alteration; and
(g) optionally testing said G-CSF analog for a desired characteristic.

[0048] In another aspect, the present disclosure relates to methods of using the present G-CSF analogs and related compositions and methods for the treatment or protection of mammals, either alone or in combination with other hematopoietic factors or drugs in the treatment of hematopoietic disorders. It is contemplated that one aspect of designing G-CSF analogs will be the goal of enhancing or modifying the characteristics non-modified G-CSF is known to have.
[0049] For example, the analogs may possess enhanced or modified activities, so, where G-CSF is useful in the treatment of (for example) neutropenia, the present compositions and methods may also be of such use.
[0050] Another example is the modification of G-CSF for the purpose of interacting more effectively when used in combination with other factors particularly in the treatment of hematopoietic disorders. One example of such combination use is to use an early-acting hematopoietic factor (i.e., a factor which acts earlier in the hematopoiesis cascade on relatively undifferentiated cells) and either simultaneously or in seriatim use of a later-acting hematopoietic factor, such as G-CSF or analog thereof (as G-CSF acts on the CFU-GM lineage in the selective stimulation of neutrophils). The methods and compositions may be useful in therapy involving such combinations or "cocktails" of hematopoietic factors.
[0051] The compositions and methods may also be useful in the treatment of leukopenia, mylogenous leukemia, severe chronic neutropenia, aplastic anemia, glycogen storage disease, mucositiitis, and other bone marrow failure states. The compositions and methods may also be useful in the treatment of hematopoietic deficits arising from chemotherapy or from radiation therapy. The success of bone marrow transplantation, or the use of peripheral blood progenitor cells for transplantation, for example, may be enhanced by application of the present compositions (proteins or nucleic acids for gene therapy) and methods. The compositions and methods may also be useful in the treatment of infectious diseases, such in the context of wound healing, burn treatment, bacteremia, septicemia, fungal infections, endocarditis, osteopyelitis, infection related to abdominal trauma, infections not responding to antibiotics, pneumonia and the treatment of bacterial inflammation may also benefit from the application of the compositions and methods. In addition, the compositions and methods may be useful in the treatment of leukemia based upon a reported ability to differentiate leukemic cells. Welte et al., PNAS-USA 82: 1526-1530 (1985). Other applications include the treatment of individuals with tumors, using the compositions and methods, optionally in the presence of receptors (such as antibod-

ies) which bind to the tumor cells. For review articles on therapeutic applications, see Lieshhke and Burgess, N.Engl.J.Med. 327: 28-34 and 99-106 (1992) both of which are herein incorporated by reference.

[0052] The compositions and methods may also be useful to act as intermediaries in the production of other moieties; for example, G-CSF has been reported to influence the production of other hematopoietic factors and this function (if ascertained) may be enhanced or modified via the present compositions and/or methods.

[0053] The compositions related to the present G-CSF analogs, such as receptors, may be useful to act as an antagonist which prevents the activity of G-CSF or an analog. One may obtain a composition with some or all of the activity of non-altered G-CSF or a G-CSF analog, and add one or more chemical moieties to alter one or more properties of such G-CSF or analog. With knowledge of the three dimensional conformation, one may forecast the best geographic location for such chemical modification to achieve the desired effect.

[0054] General objectives in chemical modification may include improved half-life (such as reduced renal, immunological or cellular clearance), altered bioactivity (such as altered enzymatic properties, dissociated bioactivities or activity in organic solvents), reduced toxicity (such as concealing toxic epitopes, compartmentalization, and selective biodistribution), altered immunoreactivity (reduced immunogenicity, reduced antigenicity or adjuvant action), or altered physical properties (such as increased solubility, improved thermal stability, improved mechanical stability, or conformational stabilization). See Francis, *Focus on Growth Factors* 3: 4-10 (May 1992) (published by Mediscript, Mountview Court, Friern Barnet Lane, London N20 OLD, UK).

[0055] The examples below are illustrative of the present invention and are not intended as a limitation. It is understood that variations and modifications will occur to those skilled in the art, and it is intended that the appended claims cover all such equivalent variations which come within the scope of the invention as claimed.

Detailed Description of the Drawings

[0056]

FIGURE 1 is an illustration of the amino acid sequence of the 174 amino acid species of G-CSF with an additional N-terminal methionine (Seq. ID No.: 1) (Seq. ID No.: 2).

FIGURE 2 is an topology diagram of the crystalline structure of G-CSF, as well as hGH, pGH, GM-CSF, INF-B, IL-2, and IL-4. These illustrations are based on inspection of cited references. The length of secondary structural elements are drawn in proportion to the number of residues. A, B, C, and D helices are labeled according to the scheme used herein for G-CSF. For INF-β, the original labeling of helices is indicated in parentheses. FIGURE 3 is an "ribbon diagram" of the three dimensional structure of G-CSF. Helix A is amino acid residues 11-39 (numbered according to Figure 1, above), helix B is amino acid residues 72-91, helix C is amino acid residues 100-123, and helix D is amino acid residues 143-173. The relatively short 3^{10} helix is at amino acid residues 45-48, and the alpha helix is at amino acid residues 48-53. Residues 93-95 form almost one turn of a left handed helix.

FIGURE 4 is a "barrel diagram" of the three dimensional structure of G-CSF. Shown in various shades of gray are the overall cylinders and their orientations for the three dimensional structure of G-CSF. The numbers indicate amino acid residue position according to FIGURE 1 above.

FIGURE 5 is a list of the coordinates used to generate a computer-aided visual image of the three-dimensional structure of G-CSF. The coordinates are set forth below. The columns correspond to separate field:

(i) Field 1 (from the left hand side) is the atom,
(ii) Field 2 is the assigned atom number,
(iii) Field 3 is the atom name (according to the periodic table standard nomenclature, with CB being carbon atom Beta, CG is Carbon atom Gamma, etc.);
(iv) Field 4 is the residue type (according to three letter nomenclature for amino acids as found in, e.g., Stryer, Biochemistry, 3d Ed., W.H. Freeman and Company, N.Y. 1988, inside back cover);
(v) Fields 5-7 are the x-axis, y-axis and z-axis positions of the atom;
(vi) Field 8 (often a "1.00") designates occupancy at that position;
(vii) Field 9 designates the B-factor;
(viii) Field 10 designates the molecule designation. Three molecules (designated a, b, and c) of G-CSF crystallized together as a unit. The designation a, b, or c indicates which coordinates are from which molecule. The number after the letter (1, 2, or 3) indicates the assigned amino acid residue position, with molecule A having assigned positions 10-175, molecule B having assigned positions 210-375, and molecule C having assigned positions 410-575. These positions were so designated so that there would be no overlap among the three molecules which crystallized together. (The "W" designation indicates water).

FIGURE 6 is a schematic representation of the strategy involved in refining the crystallization matrix for parameters

involved in crystallization. The crystallization matrix corresponds to the final concentration of the components (salts, buffers and precipitants) of the crystallization solutions in the wells of a 24 well tissue culture plate. These concentrations are produced by pipetting the appropriate volume of stock solutions into the wells of the microtiter plate. To design the matrix, the crystallographer decides on an upper and lower concentration of the component. These upper and lower concentrations can be pipetted along either the rows (e.g., A1-A6, B1-B6, C1-C6 or D1-D6) or along the entire tray (A1-D6). The former method is useful for checking reproducibility of crystal growth of a single component along a limited number of wells, whereas the later method is more useful in initial screening. The results of several stages of refinement of the crystallization matrix are illustrated by a representation of three plates. The increase in shading in the wells indicates a positive crystallization result which, in the final stages, would be X-ray quality crystals but in the initial stages could be oil droplets, granular precipitates or small crystals approximately less than 0.05 mm in size. Part A represents an initial screen of one parameter in which the range of concentration between the first well (A1) and last well (D6) is large and the concentration increase between wells is calculated as ((concentration A1)-(concentration D6))/23). Part B represents that in later stages of the crystallization matrix refinement of the concentration spread between A1 and D6 would be reduced which would result in more crystals formed per plate. Part C indicates a final stage of matrix refinement in which quality crystals are found in most wells of the plate.

Detailed Description of the Invention

[0057] The present invention grows out of the discovery of the three dimensional structure of G-CSF. This three dimensional structure has been expressed via computer program for stereoscopic viewing. By viewing this stereoscopically, structure-function relationships identified and G-CSF analogs have been designed and made.

The Overall Three Dimensional Structure of G-CSF

[0058] The G-CSF used to ascertain the structure was a non-glycosylated 174 amino acid species having an extra N-terminal methionine residue incident to bacterial expression. The DNA and amino acid sequence of this G-CSF are illustrat d in FIGURE 1.

[0059] Overall, the three dimensional structure of G-CSF is predominantly helical, with 103 of the 175 residues forming a 4-alpha-helical bundle. The only other secondary structure is found in the loop between the first two long helices where a 4 residue 3^{10} helix is immediately followed by a 6 residue alpha helix. As shown in FIGURE 2, the overall structure has been compared with the structure reported for other proteins: growth hormone (Abdel-Meguid et al., PNAS-USA 84: 6434 (1987) and Vos et al., Science 255: 305-312 (1992)), granulocyte macrophage colony stimulating factor (Diederichs et al., Science 254: 1779-1782 (1991), interferon-β (Senda et al., EMBO J. 11: 3193-3201 (1992)), interleukin-2 (McKay Science 257: 1673-1677 (1992)) and interleukin-4 (Powers et al., Science 256: 1673-1677 (1992), and Smith et al., J. Mol. Biol. 224: 899-904 (1992)). Structural similarity among these growth factors occurs despite the absence of similarity in their amino acid sequences.

[0060] Presently, the structural information was correlation of G-CSF biochemistry, and this can be summarized as follows (with sequence position 1 being at the N-terminus):

Sequence Position	Description of Structure	Analysis
1-10	Extended chain	Deletion causes no loss of biological activity
Cys 18	Partially buried	Reactive with DTNB and Thimersosol but not with iodo-acetate
34	Alternative splice site	Insertion reduces biological activity
20-47 (inclusive)	Helix A, first disulfide and portion of AB helix	Predicted receptor binding region based on neutralizing antibody data
20, 23, 24	Helix A	Single alanine mutation of residue(s) reduces biological activity. Predicted receptor binding (Site B).
165-175 (inclusive)	Carboxy terminus	Deletion reduces biological activity

[0061] This biochemical information, having been gleaned from antibody binding studies, see Layton et al., Biochemistry 266: 23815-23823 (1991), was superimposed on the three-dimensional structure in order to design G-CSF analogs. The design, preparation, and testing of these G-CSF analogs is described in Example 1 below.

EXAMPLE 1

[0062] This Example describes the preparation of crystalline G-CSF, the visualization of the three dimensional structure of recombinant human G-CSF via computer-generated image, the preparation of analogs, using site-directed mutagenesis or nucleic acid amplification methods, the biological assays and HPLC analysis used to analyze the G-CSF analogs, and the resulting determination of overall structure/function relationships. All cited publications are herein incorporated by reference.

A. Use of Automated Crystallization

[0063] The need for a three-dimensional structure of recombinant human granulocyte colony stimulating factor (r-hu-G-CSF), and the availability of large quantities of the purified protein, led to methods of crystal growth by incomplete factorial sampling and seeding. Starting with the implementation of incomplete factorial crystallization described by Jancarik and Kim· J. Appl. Crystallogr. 24: 409 (1991) solution conditions that yielded oil droplets and birefringence aggregates were ascertained. Also, software and hardware of an automated pipetting system were modified to produce some 400 different crystallization conditions per day. Weber, J. Appl. Crystallogr. 20: 366-373 (1987). This procedure led to a crystallization solution which produced r-hu-G-CSF crystals.

[0064] The size, reproducibility and quality of the crystals was improved by a seeding method in which the number of "nucleation initiating units" was estimated by serial dilution of a seeding solution. These methods yielded reproducible growth of 2.0 mm r-hu-G-CSF crystals. The space group of these crystals is $P2_12_12_1$ with cell dimensions of a=90 Å, b=110 Å and c=49 Å, and they diffract to a resolution of 2.0 Å.

1. Overall Methodology

[0065] To search for the crystallizing conditions of a new protein, Carter and Carter, J. Biol. Chem. 254: 12219-12223 (1979) proposed the incomplete factorial method. They suggested that a sampling of a large number of randomly selected, but generally probable, crystallizing conditions may lead to a successful combination of reagents that produce protein crystallization. This idea was implemented by Jancarik and Kim, J. Appl. Crystallogr. 24: 409(1991), who described 32 solutions for the initial crystallization trials which cover a range of pH, salts and precipitants. Here we describe an extension of their implementation to an expanded set of 70 solutions. To minimize the human effort and error of solution preparation, the method has been programmed for an automatic pipetting machine.

[0066] Following Weber's method of successive automated grid searching (SAGS), J.Cryst. Growth 90: 318-324(1988), the robotic system was used to generate a series of solutions which continually refined the crystallization conditions of temperature, pH, salts and precipitant. Once a solution that could reproducibly grow crystals was determined, a seeding technique which greatly improved the quality of the crystals was developed. When these methods were combined, hundreds of diffraction quality crystals (crystals diffracting to at least about 2.5 Angstroms, preferably having at least portions diffracting to below 2 Angstroms, and more preferably, approximately 1 Angstrom) were produced in a few days.

[0067] Generally, the method for crystallization, which may be used with any protein one desires to crystallize, comprises the steps of:

(a) combining aqueous aliquots of the desired protein with either (i) aliquots of a salt solution, each aliquot having a different concentration of salt; or (ii) aliquots of a precipitant solution, each aliquot having a different concentration of precipitant, optionally wherein each combined aliquot is combined in the presence of a range of pH;
(b) observing said combined aliquots for precrystalline formations, and selecting said salt or precipitant combination and said pH which is efficacious in producing precrystalline forms, or, if no precrystalline forms are so produced, increasing the protein starting concentration of said aqueous aliquots of protein;
(c) after said salt or said precipitant concentration is selected, repeating step (a) with said previously unselected solution in the presence of said selected concentration; and
(d) repeating step (b) and step (a) until a crystal of desired quality is obtained.

[0068] The above method may optionally be automated, which provides vast savings in time and labor. Preferred protein starting concentrations are between 10mg/ml and 20mg/ml, however this starting concentration will vary with the protein (the G-CSF below was analyzed using 33mg/ml). A preferred range of salt solution to begin analysis with is

(NaCl) of 0-2.5M. A preferred precipitant is polyethylene glycol 8000, however, other precipitants include organic solvents (such as ethanol), polyethylene glycol molecules having a molecular weight in the range of 500-20,000, and other precipitants known to those skilled in the art. The preferred pH range is pH 4.5 , 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, and 9.0. Precrystallization forms include oils, birefringement precipitants, small crystals (< approximately 0.05 mm), medium crystals (approximately 0.5 to .5 mm) and large crystals (> approximately 0.5 mm). The preferred time for waiting to see a crystalline structure is 48 hours, although weekly observation is also preferred, and generally, after about one month, a different protein concentration is utilized (generally the protein concentration is increased). Automation is preferred, using the Accuflex system as modified. The preferred automation parameters are described below.

[0069] Generally, protein with a concentration between 10 mg/ml and 20 mg/ml was combined with a range of NaCl solutions from 0-2.5 M, and each such combination was performed (separately) in the presence of the above range of concentrations. Once a precrystallization structure is observed, that salt concentration and pH range are optimized in a separate experiment, until the desired crystal quality is achieved. Next, the precipitant concentration, in the presence of varying levels of pH is also optimized. When both are optimized, the optimal conditions are performed at once to achieve the desired result (this is diagrammed in FIGURE 6).

a. Implementation of an automated pipetting system

[0070] Drops and reservoir solutions were prepared by an Accuflex pipetting system (ICN Pharmaceuticals, Costa Mesa, CA) which is controlled by a personal computer that sends ASCII codes through a standard serial interface. The pipetter samples six different solutions by means of a rotating valve and pipettes these solutions onto a plate whose translation in a x-y coordinate system can be controlled. The vertical component of the system manipulates a syringe that is capable both of dispensing and retrieving liquid.

[0071] The software provided with the Accuflex was based on the SAGS method as proposed by Cox and Weber, J.Appl. Crystallogr. 20: 366-373 (1987). This method involves the systematic variation of two major crystallization parameters, pH and precipitant concentration, with provision to vary two others. While building on these concepts, the software used here provided greater flexibility in the design and implementation of the crystallization solutions used in the automated grid searching strategy. As a result of this flexibility the present software also created a larger number of different solutions. This is essential for the implementation of the incomplete factorial method as described in that section below.

[0072] To improve the speed and design of the automated grid searching strategy, the Accuflex pipetting system required software and hardware modifications. The hardware changes allowed the use of two different micro-titer trays, one used for handing drop and one used for sitting drop experiments, and a Plexiglas tray which held 24 additional buffer, salt and precipitant solutions. These additional solutions expanded the grid of crystallizing conditions that could be surveyed.

[0073] To utilize the hardware modifications, the pipetting software was written in two subroutines; one subroutine allows the crystallographer to design a matrix of crystallization solutions based on the concentrations of their components and the second subroutine to translate these concentrations into the computer code which pipettes the proper volumes of the solutions into the crystallization trays. The concentration matrices can be generated by either of two programs. The first program (MRF, available from Amgen, Inc., Thousand Oaks, CA) refers to a list of stock solution concentrations supplied by the crystallographer and calculates the required volume to be pipette to achieve the designated concentration. The second method, which is preferred, incorporates a spread sheet program (Lotus) which can be used to make more sophisticated gradients of precipitants or pH. The concentration matrix created by either program is interpreted by the control program (SUX, a modification of the program found in the Accuflex pipetter originally and available from Amgen, Inc., Thousand Oaks, CA) and the wells are filled accordingly.

b. Implementation of the Incomplete Factorial Method

[0074] The convenience of the modified pipetting system for preparing diverse solutions improved the implementation of an expanded incomplete factorial method. The development of a new set of crystallization solutions having "random" components was generated using the program INFAC, Carter et al., J.Cryst. Growth 90: 60-73(1988) which produced a list containing 96 random combinations of one factor from three variables. Combinations of calcium and phosphate which immediately precipitated were eliminated, leaving 70 distinct combinations of precipitants, salts and buffers. These combinations were prepared using the automated pipetter and incubated for 1 week. The mixtures were inspected and solutions which formed precipitants were prepared again with lower concentrations of their components. This was repeated until all wells were clear of precipitant.

c. Crystallization of r-hu-G-CSF

[0075] Several different crystallization strategies were used to find a solution which produced x-ray quality crystals. These strategies included the use of the incomplete factorial method, refinement of the crystallization conditions using successive automated grid searches (SAGS), implementation of a seeding technique and development of a crystal production procedure which yielded hundreds of quality crystals overnight. Unless otherwise noted the screening and production of r-hu-G-CSF crystals utilized the hanging drop vapor diffusion method. Afinsen et al., Physical principles of protein crystallization. In: Eisenberg (ed.), Advances in Protein Chemistry 41: 1-33 (1991).

[0076] The initial screening for crystallization conditions of r-hu-G-CSF used the Jancarik and Kim, J.Appl.Crystallogr. 24: 409(1991) incomplete factorial method which resulted in several solutions that produced "precrystallization" results. These results included birefringent precipitants, oils and very small crystals (< .05 mm). These precrystallizations solutions then served as the starting points for systematic screening.

[0077] The screening process required the development of crystallization matrices. These matrices corresponded to the concentration of the components in the crystallization solutions and were created using the IBM-PC based spread sheet Lotus™ and implemented with the modified Accuflex pipetting system. The strategy in designing the matrices was to vary one crystallization condition (such as salt concentration) while holding the other conditions such as pH, and precipitant concentration constant. At the start of screening, the concentration range of the varied condition was large but the concentration was successively refined until all wells in the micro-titer tray produced the same crystallization result. These results were scored as follows: crystals, birefringement precipitate, granular precipitate, oil droplets and amorphous mass. If the concentration of a crystallization parameter did not produce at least a precipitant, the concentration of that parameter was increased until a precipitant formed. After each tray was produced, it was left undisturbed for at least two days and then inspected for crystal growth. After this initial screening, the trays were then inspected on a weekly basis.

[0078] From this screening process, two independent solutions with the same pH and precipitant but differing in salts (MgCl, $LiSO_4$) were identified which produced small (0.1 x 0.05 x 0.05 mm) crystals. Based on these results, a new series of concentration matrices were produced which varied MgCl with respect to $LiSO_4$ while keeping the other crystallization parameters constant. This series of experiments resulted in identification of a solution which produced diffraction quality crystals (> approximately 0.5 mm) in about three weeks. To find this crystallization growth solution (100 mM Mes pH 5.8, 380 mM $MgCl_2$, 220 mM LiSO4 and 8% PEG 8k) approximately 8,000 conditions had been screened which consumed about 300 mg of protein.

[0079] The size of the crystals depended on the number of crystals forming per drop. Typically 3 to 5 crystals would be formed with average size of (1.0 x 0.7 x 0.7 mm). Two morphologies which had an identical space group ($P2_12_12_1$) and unit cell dimensions a=90.2, b=110.2, c=49.5 were obtained depending on whether or not seeding (see below) was implemented. Without seeding, the r-hu-G-CSF crystals had one long flat surface and rounded edges.

[0080] When seeding was employed, crystals with sharp faces were observed in the drop within 4 to 6 hours (0.05 by 0.05 by 0.05 mm). Within 24 hours, crystals had grown to (0.7 by 0.7 by 0.7 mm) and continued to grow beyond 2 mm depending on the number of crystals forming in the drop.

d. Seeding and determination of nucleation initiation sites.

[0081] The presently provided method for seeding crystals establishes the number of nucleation initiation units in each individual well used (here, after the optimum conditions for growing crystals had been determined). The method here is advantageous in that the number of "seeds" affects the quality of the crystals, and this in turn affects the degree of resolution. The present seeding here also provides advantages in that with seeding, G-CSF crystal grows in a period of about 3 days, whereas without seeding, the growth takes approximately three weeks.

[0082] In one series of production growth (see methods), showers of small but well defined crystals were produced overnight (<0.01 x 0.01 x0.01 mm). Crystallization conditions were followed as described above except that a pipette tip employed in previously had been reused. Presumably, the crystal showering effect was caused by small nucleation units which had formed in the used tip and which provided sites of nucleation for the crystals. Addition of a small amount (0.5 ul) of the drops containing the crystal showers to a new drop under standard production growth conditions resulted in a shower of crystals overnight. This method was used to produce several trays of drops containing crystal showers which we termed "seed stock".

[0083] The number of nucleation initiation units (NIU) contained within the "seed stock" drops was estimated to attempt to improve the reproducibility and quality of the r-hu-GCSF crystals. To determine the number of NIU in the "seed stock", an aliquot of the drop was serially diluted along a 96 well microtiter plate. The microtiter plate was prepared by adding 50 ul of a solution containing equal volumes of r-hu-G-CSF (33 mg/ml) and the crystal growth solution (described above) in each well. An aliquot (3 ul) of one of the "seed stock" drops was transferred to the first well of the microtiter plate. The solution in the well was mixed and 3 ul was then transferred to the next well along the row of the

microtiter plate. Each row of the microtiter plate was similarly prepared and the tray was sealed with plastic tape. Overnight, small crystals formed in the bottom of the wells of the microtiter plate and the number of crystals in the wells were correlated to the dilution of the original "seed stock". To produce large single crystals, the "seed stock" drop was appropriately diluted into fresh CGS and then an aliquot of this solution containing the NIU was transferred to a drop

[0084] Once crystallization conditions had been optimized, crystals were grown in a production method in which 3 ml each of CGS and r-hu-G-CSF (33 mg/ml) were mixed to create 5 trays (each having 24 wells). This method included the production of the refined crystallization solution in liter quantities, mixing this solution with protein and placing the protein/crystallization solution in either hanging drop or sitting drop trays. This process typically yielded 100 to 300 quality crystals (>0.5 mm) in about 5 days.

e. Experimental Methods

Materials

[0085] Crystallographic information was obtained starting with r-hu-met-G-CSF with the amino acid sequence as provided in FIGURE 1 with a specific activity of 1.0 +/- 0.6 x 10^8U/mg (as measured by cell mitogenesis assay in a 10 mM acetate buffer at pH 4.0 (in Water for Injection) at a concentration of approximately 3 mg/ml solution was concentrated with an Amicon concentrator at 75 psi using a YM10 filter. The solution was typically concentrated 10 fold at 4°C and stored for several months.

Initial Screening

[0086] Crystals suitable for X-ray analysis were obtained by vapor-diffusion equilibrium using hanging drops. For preliminary screening, 7 ul of the protein solution at 33 mg/ml (as prepared above) was mixed with an equal volume of the well solution, placed on siliconized glass plates and suspended over the well solution utilizing Linbro tissue culture plates (Flow Laboratories, McLean, Va). All of the pipetting was performed with the Accuflex pipetter, however, trays were removed from the automated pipetter after the well solutions had been created and thoroughly mixed for at least 10 minutes with a table top shaker. The Linbro trays were then returned to the pipetter which added the well and protein solutions to the siliconized cover slips. The cover slips were then inverted and sealed over 1 ml of the well solutions with silicon grease.

[0087] The components of the automated crystallization system are as follows. A PC-DOS computer system was used to design a matrix of crystallization solutions based on the concentration of their components. These matrices were produced with either MRF of the Lotus spread sheet (described above). The final product of these programs is a data file. This file contains the information required by the SUX program to pipette the appropriate volume of the stock solutions to obtain the concentrations described in the matrices. The SUX program information was passed through a serial I/O port and used to dictate to the Accuflex pipetting system the position of the valve relative to the stock solutions, the amount of solution to be retrieved, and then pipetted into the wells of the microtiter plates and the X-Y position of each well (the column/row of each well). Addition information was transmitted to the pipetter which included the Z position (height) of the syringe during filling as well as the position of a drain where the system pauses to purge the syringe between fillings of different solutions. The 24 well microtiter plate (either Linbro or Cryschem) and cover slip holder was placed on a plate which was moved in the X-Y plane. Movement of the plate allowed the pipetter to position the syringe to pipette into the wells. It also positioned the coverslips and vials and extract solutions from these sources. Prior the pipetting, the Linbro microtiter plates had a thin film of grease applied around the edges of the wells. After the crystallization solutions were prepared in the wells and before they were transferred to the cover slips, the microtiter plate was removed from the pipetting system, and solutions were allowed to mix on a table top shaker for ten minutes. After mixing, the well solution was either transferred to the cover slips (in the case of the hanging drop protocol) or transferred to the middle post in the well (in the case of the sitting drop protocol). Protein was extracted from a vial and added to the coverslip drop containing the well solution (or to the post). Plastic tape was applied to the top of the Cryschem plate to seal the wells.

Production Growth

[0088] Once conditions for crystallization had been optimized, crystal growth was performed utilizing a "production" method. The crystallization solution which contained 100 mM Mes pH 5.8, 380 mM $MgCl_2$, 220 mM $LiSO_4$, and 8% PEG 8K was made in 1 liter quantities. Utilizing an Eppindorf syringe pipetter, 1 ml aliquots of this solution were pipetted into each of the wells of the Linbro plate. A solution containing 50% of this solution and 50% G-CSF (33 mg/ml) was mixed and pipetted onto the siliconized cover slips. Typical volumes of these drops were between 50 and 100 ul and because of the large size of these drops, great care was taken in flipping the coverslips and suspending the drops over

the wells.

Data Collection

[0089] The structure has been refined with X-PLOR (Bruniger, X-PLOR version 3.0, A system for crystallography and NMR, Yale University, New Haven CT) against 2.2Å data collected on an R-AXIS (Molecular Structure, Corp. Houston, TX) imaging plate detector.

f. Observations

[0090] As an effective recombinant human therapeutic, r-hu-G-CSF has been produced in large quantities and gram levels have been made available for structural analysis. The crystallization methods provided herein are likely to find other applications as other proteins of interest become available. This method can be applied to any crystallographic project which has large quantities of protein (approximately >200 mg). As one skilled in the art will recognize, the present materials and methods may be modified and equivalent materials and methods may be available for crystallization of other proteins.

B. Computer Program For Visualizing The Three Dimensional Structure of G-CSF

[0091] Although diagrams, such as those in the Figures herein, are useful for visualizing the three dimensional structure of G-CSF, a computer program which allows for stereoscopic viewing of the molecule is contemplated as preferred. This stereoscopic viewing, or "virtual reality" as those in the art sometimes refer to it, allows one to visualize the structure in its three dimensional form from every angle in a wide range of resolution, from macromolecular structure down to the atomic level. The computer programs contemplated herein also allow one to change perspective of the viewing angle of the molecule, for example by rotating the molecule. The contemplated programs also respond to changes so that one may, for example, delete, add, or substitute one or more images of atoms, including entire amino acid residues, or add chemical moieties to existing or substituted groups, and visualize the change in structure.

[0092] Other computer based systems may be used; the elements being: (a) a means for entering information, such as orthogonal coordinates or other numerically assigned coordinates of the three dimensional structure of G-CSF; (b) a means for expressing such coordinates, such as visual means so that one may view the three dimensional structure and correlate such three dimensional structure with the composition of the G-CSF molecule, such as the amino acid composition; (c) optionally, means for entering information which alters the composition of the G-CSF molecule expressed, so that the image of such three dimensional structure displays the altered composition.

[0093] The coordinates for the preferred computer program used are presented in FIGURE 5. The preferred computer program is Insight II, version 4, available from Biosym in San Diego, CA. For the raw crystallographic structure, the observed intensities of the diffraction data ("F-obs") and the orthogonal coordinates are also deposited in the Protein Data Bank, Chemistry Department, Brookhaven National Laboratory, Upton, New York 19723, USA and these are herein incorporated by reference.

[0094] Once the coordinates are entered into the Insight II program, one can easily display the three dimensional G-CSF molecule representation on a computer screen. The preferred computer system for display is Silicon Graphics 320 VGX (San Diego, CA). For stereoscopic viewing, one may wear eyewear (Crystal Eyes, Silicon Graphics) which allows one to visualize the G-CSF molecule in three dimensions stereoscopically, so one may turn the molecule and envision molecular design.

[0095] Thus, the present invention provides a method of designing or preparing a G-CSF analog with the aid of a computer comprising:

(a) providing said computer with the means for displaying the three dimensional structure of a G-CSF molecule including displaying the composition of moieties of said G-CSF molecule, preferably displaying the three dimensional location of each amino acid, and more preferably displaying the three dimensional location of each atom of a G-CSF molecule;
(b) viewing said display;
(c) selecting a site on said display for alteration in the composition of said molecule or the location of a moiety; and
(d) preparing a G-CSF analog with such alteration.

[0096] The alteration may be selected based on the desired structural characteristics of the end-product G-CSF analog, and considerations for such design are described in more detail below. Such considerations include the location and compositions of hydrophobic amino acid residues, particularly residues internal to the helical structures of a G-CSF molecule which residues, when altered, alter the overall structure of the internal core of the molecule and may prevent

receptor binding; the location and compositions of external loop structures, alteration of which may not affect the overall structure of the G-CSF molecule.

[0097] FIGURES 2-4 illustrate the overall three dimensional conformation in different ways. The topological diagram, the ribbon diagram, and the barrel diagram all illustrate aspects of the conformation of G-CSF.

[0098] FIGURE 2 illustrates a comparison between G-CSF and other molecules. There is a similarity of architecture, although these growth factors differ in the local conformations of their loops and bundle geometrics. The up-up-down-down topology with two long crossover connections is conserved, however, among all six of these molecules, despite the dissimilarity in amino acid sequence.

[0099] FIGURE 3 illustrates in more detail the secondary structure of recombinant human G-CSF. This ribbon diagram illustrates the handedness of the helices and their positions relative to each other.

[0100] FIGURE 4 illustrates in a different way the conformation of recombinant human G-CSF. This "barrel" diagram illustrates the overall architecture of recombinant human G-CSF.

C. Preparation of Analogs Using M13 Mutagenesis

[0101] This example relates to the preparation of G-CSF analogs using site directed mutagenesis techniques involving the single stranded bacteriophage M13, according to methods published in PCT Application No. WO 85/00817 (Souza et al., published February 28, 1985, herein incorporated by reference). This method essentially involves using a single-stranded nucleic acid template of the non-mutagenized sequence, and binding to it a smaller oligonucleotide containing the desired change in the sequence. Hybridization conditions allow for non-identical sequences to hybridize and the remaining sequence is filled in to be identical to the original template. What results is a double stranded molecule, with one of the two strands containing the desired change. This mutagenized single strand is separated, and used itself as a template for its complementary strand. This creates a double stranded molecule with the desired change.

[0102] The original G-CSF nucleic acid sequence used is presented in FIGURE 1, and the oligonucleotides containing the mutagenized nucleic acid(s) are presented in Table 2. Abbreviations used herein for amino acid residues and nucleotides are conventional, see Stryer, Biochemistry, 3d Ed., W.H. Freeman and Company, N.Y., N.Y. 1988, inside back cover.

[0103] The original G-CSF nucleic acid sequence was first placed into vector M13mp21. The DNA from single stranded phage M13mp21 containing the original G-CSF sequence was then isolated, and resuspended in water. For each reaction, 200 ng of this DNA was mixed with a 1.5 pmole of phosphorylated oligonucleotide (Table 2) and suspend d in 0.1M Tris, 0.01M $MgCl_2$, 0.005M DTT, 0.1mM ATP, pH 8.0. The DNAs were annealed by heating to 65°C and slowly cooling to room temperature.

[0104] Once cooled, 0.5mM of each ATP, dATP, dCTP, dGTP, TTP, 1 unit of T4 DNA ligase and 1 unit of Klenow fragment of E. coli polymerase 1 were added to the 1 unit of annealed DNA in 0.1M Tris, 0.025M NaCl, 0.01M $MgCl_2$, 0.01M DTT, pH 7.5.

[0105] The now double stranded, closed circular DNA was used to transfect E. coli without further purification. Plaques were screened by lifting the plaques with nitrocellulose filters, and then hybridizing the filters with single stranded DNA end-labeled with P^{32} for 1 hour at 55-60°C. After hybridization, the filters were washed at 0-3°C below the melt temperature of the oligo (2°C for A-T, 4°C for G-C) which selectively left autoradiography signals corresponding to plaques with phage containing the mutated sequence. Positive clones were confirmed by sequencing.

[0106] Set forth below are the oligonucleotides used for each G-CSF analog prepared via the M13 mutagenesis method. The nomenclature indicates the residue and the position of the original amino acid (e.g., Lysine at position 17), and the residue and position of the substituted amino acid (e.g., arginine 17). A substitution involving more than one residue is indicated via superscript notation, with commas between the noted positions or a semicolon indicating different residues. Deletions with no substitutions are so noted. The oligonucleotide sequences used for M13-based mutagenesis are next indicated; these oligonucleotides were manufactured synthetically, although the method of preparation is not critical, any nucleic acid synthesis method and/or equipment may be used. The length of the oligo is also indicated. As indicated above, these oligos were allowed to contact the single stranded phage vector, and then single nucleotides were added to complete the G-CSF analog nucleic acid sequence.

Table 2

G-CSF ANALOGS	SEQUENCES (5'-> 3')	Length (nucleotide)	Seq. ID
Lys^{17}->Arg^{17}	CTT TCT GCT GCG TTG TCT GGA ACA	24	3
Lys^{24}->Arg^{24}	ACA GGT TCG TCG TAT CCA GGG TG	23	4
Lys^{35}->Arg^{35}	CAC TGC AAG AAC GTC TGT GCG CT	23	5
Lys^{41}->Arg^{41}	CGC TAC TTA CCG TCT GTG CCA TC	23	6
$Lys^{17,24,35}$-> $Arg^{17,24,35}$	CTT TCT GCT GCG TTG TCT GGA ACA	24	7
	ACA GGT TCG TCG TAT CCA GGG TG	23	8
	CAC TGC AAG AAC GTC TGT GCG CT	23	9
$Lys^{17,24,41}$-> $Arg^{17,24,41}$	CTT TCT GCT GCG TTG TCT GGA ACA	24	10
	ACA GGT TCG TCG TAT CCA GGG TG	23	11
	CGC TAC TTA CCG TCT GTC CCA TC	23	12
$Lys^{17,35,41}$-> $Arg^{17,35,41}$	CTT TCT GCT GCG TTG TCT GGA ACA	24	13
	CAC TGC AAG AAC GTC TGT GCG CT	23	14
	CGC TAC TTA CCG TCT GTG CCA TC	23	15
$Lys^{24,35,41}$-> $Arg^{24,35,41}$	ACA GGT TCG TCG TAT CCA GGG TG	23	16
	CAC TGC AAG AAC GTC TGT GCG CT	23	17
	CGC TAC TTA CCG TCT GTG CCA TC	23	18

Table 2 (con't)

G-CSF ANALOGS	SEQUENCES (5'-> 3')	Length (nucleotide)	Seq. ID
$Lys^{17,24,35,41}$-> $Arg^{17,24,35,41}$	CTT TCT GCT GCG TTG TCT GGA ACA	24	19
	ACA GGT TCG TCG TAT CCA GGG TG	23	20
	CAC TGC AAG AAC GTC TGT GCG CT	23	21
	CGC TAC TTA CCG TCT GTG CCA TC	23	22
Cys^{18}->Ala^{18}	TCT GCT GAA AGC TCT GGA ACA GG	23	23
Gln^{68}->Glu^{68}	CTT GTC CAT CTG AAG CTC TTC AG	23	24
$Cys^{37,43}$-> $Ser^{37,43}$	GAA AAA CTG TCC GCT ACT TAC AAA CTG TCC CAT CCG G	37	25
Gln^{26}->Ala^{26}	TTC GTA AAA TCG CGG GTG ACG G	22	26
Gln^{174}->Ala^{174}	TCA TCT GGC TGC GCC GTA ATA G	22	27
Arg^{170}->Ala^{170}	CCG TGT TCT GGC TCA TCT GGC T	22	28
Arg^{167}->Ala^{167}	GAA GTA TCT TAC GCT GTT CTG CGT	24	29
Deletion 167	GAA GTA TCT TAC TAA GTT CTG CGT C	25	30
Lys^{41}->Ala^{41}	CGC TAC TTA CGC ACT GTG CCA T	22	31
His^{44}->Lys^{44}	CAA ACT GTG CAA GCC GGA AGA G	22	32
Glu^{47}->Ala^{47}	CAT CCG GAA GCA CTG GTA CTG C	22	33

Table 2 (con't)

G-CSF ANALOGS	SEQUENCES(5'-> 3')	Length(nucleotide)	Seq. ID
Arg^{23}->Ala^{23}	GGA ACA GGT TGC TAA AAT CCA GG	23	34
Lys^{24}->Ala^{24}	GAA CAG GTT CGT GCG ATC CAG GGT G	25	35
Glu^{20}->Ala^{20}	GAA ATG TCT GGC ACA GGT TCG T	22	36
Asp^{28}->Ala^{28}	TCC AGG GTG CCG GTG CTG C	19	37
Met^{127}->Glu^{127}	AAG AGC TCG GTG AGG CAC CAG CT	23	38
Met^{138}->Glu^{138}	CTC AAG GTG CTG AGC CGG CAT TC	23	39
Met^{127}->Leu^{127}	GAG CTC GGT CTG GCA CCA GC	20	40
Met^{138}->Leu^{138}	TCA AGG TGC TCT GCC GGC ATT	21	41
Ser^{13}->Ala^{13}	TCT GCC GCA AGC CTT TCT GCT GA	23	42
Lys^{17}->Ala^{17}	CTT TCT GCT GGC ATG TCT GGA ACA	24	43
Gln^{121}->Ala^{121}	CTA TTT GGC AAG CGA TGG AAG AGC	24	44
Glu^{124}->Ala^{124}	CAG ATG GAA GCG CTC GGT ATG	21	45

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Table 2 (con't)

G-CSF ANALOGS	SEQUENCES (5'-> 3')	Length (nucleotide)	Seq. ID
$Met^{127,138}$-> $Leu^{127,138}$	GAG CTC GGT CTG GCA CCA GC TCA AGG TGC TCT GCC GGC ATT	20 21	46 47
**Glu^{20}->Ala^{20}; Ser^{13}->Gly^{13}	GAA ATG TCT GGC ACA GGT TCG T	22	48

** This analog came about during the preparation of G-CSF analog Glu^{20}->Ala^{20}. As several clones were being sequenced to identify the Glu^{20}->Ala^{20} analog, the Glu^{20}->Ala^{20}; Ser^{13}->Gly^{13} analog was identified. This double mutant was the result of an *in vitro* Klenow DNA polymerase reaction mistake.

D. Preparation of G-CSF Analogs Using DNA Amplification

[0107] This example relates to methods for producing G-CSF analogs using a DNA amplification technique. Essentially, DNA encoding each analog was amplified in two separate pieces, combined, and then the total sequence itself amplified. Depending upon where the desired change in the original G-CSF DNA was to be made, internal primers were used to incorporate the change, and generate the two separate amplified pieces. For example, for amplification of the 5' end of the desired analog DNA, a 5' flanking primer (complementary to a sequence of the plasmid upstream from the G-CSF original DNA) was used at one end of the region to be amplified, and an internal primer, capable of hybridizing to the original DNA but incorporating the desired change, was used for priming the other end. The resulting amplified region stretched from the 5' flanking primer through the internal primer. The same was done for the 3' terminus, using a 3' flanking primer (complementary to a sequence of the plasmid downstream from the G-CSF original DNA) and an internal primer complementary to the region of the intended mutation. Once the two "halves" (which may or may not be equal in size, depending on the location of the internal primer) were amplified, the two "halves" were allowed to connect. Once connected, the 5' flanking primer and the 3' flanking primer were used to amplify the entire sequence containing the desired change.

[0108] If more than one change is desired, the above process may be modified to incorporate the change into the internal primer, or the process may be repeated using a different internal primer. Alternatively, the gene amplification process may be used with other methods for creating changes in nucleic acid sequence, such as the phage based mutagenesis technique as described above. Examples of process for preparing analogs with more than one change are described below.

[0109] To create the G-CSF analogs described below, the template DNA used was the sequence as in FIGURE 1 plus certain flanking regions (from a plasmid containing the G-CSF coding region). These flanking regions were used as the 5' and 3' flanking primers and are set forth below. The amplification reactions were performed in 40 ul volumes containing 10 mM Tris-HCl, 1.5 mM $MgCl_2$, 50 mM KCl, 0.1 mg/ml gelatin, pH 8.3 at 20°C. The 40 ul reactions also contained 0.1mM of each dNTP, 10 pmoles of each primer, and 1 ng of template DNA. Each amplification was repeated for 15 cycles. Each cycle consisted of 0.5 minutes at 94°C, 0.5 minutes at 50°C, and 0.75 minutes at 72°C. Flanking primers were 20 nucleotides in length and internal primers were 20 to 25 nucleotides in length. This resulted in multiple copies of double stranded DNA encoding either the front portion or the back portion of the desired G-CSF analog.

[0110] For combining the two "halves," one fortieth of each of the two reactions was combined in a third DNA amplification reaction. The two portions were allowed to anneal at the internal primer location, as their ends bearing the mutation were complementary, and following a cycle of polymerization, give rise to a full length DNA sequence. Once so annealed, the whole analog was amplified using the 5' and 3' flanking primers. This amplification process was repeated for 15 cycles as described above.

[0111] The completed, amplified analog DNA sequence was cleaved with XbaI and XhoI restriction endonuclease to produce cohesive ends for insertion into a vector. The cleaved DNA was placed into a plasmid vector, and that vector was used to transform E. coli. Transformants were challenged with kanamycin at 50 ug/ml and incubated at 30°C. Production of G-CSF analog protein was confirmed by polyacrylamide gel electrophoresis of a whole cell lysate. The presence of the desired mutation was confirmed by DNA sequence analysis of plasmid purified from the production isolate. Cultures were then grown, and cells were harvested, and the G-CSF analogs were purified as set forth below.

[0112] Set forth below in Table 3 are the specific primers used for each analog made using gene amplification.

Table 3

Analog Seq. ID	Internal Primer(5'->3')	
His^{44}->Ala^{44}	5'primer-TTCCGGAGCGCACAGTTTG	49
	3'primer-CAAACTGTGGGCTCCGGAAGAGC	50
Thr^{117}->Ala^{117}	5'primer-ATGCCAAATTGCAGTAGCAAAG	51
	3'primer-CTTTGCTACTGCAATTTGGCAACA	52
Asp^{110}->Ala^{110}	5'primer-ATCAGCTACTGCTAGCTGCAGA	53
	3'primer-TCTGCAGCTAGCAGTAGCTGACT	54
Gln^{21}->Ala^{21}	5'primer-TTACGAACCGCTTCCAGACATT	55
	3'primer-AATGTCTGGAAGCGGTTCGTAAAAT	56

Table 3 (continued)

Analog Seq. ID	Internal Primer(5'->3')	
Asp^{113}->Ala^{113}	5'primer-GTAGCAAATGCAGCTACATCTA	57
	3'primer-TAGATGTAGCTGCATTTGCTACTAC	58
His^{53}->Ala^{53}	5'primer-CCAAGAGAAGCACCCAGCAG	59
	3'primer-CTGCTGGGTGCTTCTCTTGGGA	60
For each analog, the following 5' flanking primer was used:		
	5'-CACTGGCGGTGATAATGAGC	61
For each analog, the following 3' flanking primer was used:		
	3'-GGTCATTACGGACCGGATC	62

1. Consfruction of Double Mutation

[0113] To make G-CSF analog $Gln^{12,21}$->$Glu^{12,21}$, two separate DNA amplifications were conducted to create the two DNA mutations. The template DNA used was the sequence as in FIGURE 1 plus certain flanking regions (from a plasmid containing the G-CSF coding region). The precise sequences are listed below. Each of the two DNA amplification reactions were carried out using a Perkin Elmer/Cetus DNA Thermal Cycler. The 40 ul reaction mix consisted of 1X PCR Buffer (Cetus), 0.2 mM each of the 4 dXTPs (Cetus), 50 pmoles of each primer oligonucleotide, 2 ng of G-CSF template DNA (on a plasmid vector), and 1 unit of Taq polymerase (Cetus). The amplification process was carried out for 30 cycles. Each cycle consisted of 1minute at 94°C, 2 minutes at 50°C, and 3 minutes at 72°C.

[0114] DNA amplification "A" used the oligonucleotides:
5' CCACTGGCGGTGATACTGAGC 3' (Seq. ID 63) and
5' AGCAGAAAGCTTTCCGGCAGAGAAGAAGCAGGA 3' (Seq. ID 64)

[0115] DNA amplification "B" used the oligonucleotides:
5' GCCGCAAAGCTTTCTGCTGAAATGTCTGGAAGAGGTTCGTAAAATCCAGGGTGA 3' (Seq. ID 65) and
5' CTGGAATGCAGAAGCAAATGCCGGCATAGCACCTTCAGTCGGTTGCAGAGCTGGTGCCA 3' (Seq. ID 66)

[0116] From the 109 base pair double stranded DNA product obtained after DNA amplification "A", a 64 base pair XbaI to HindIII DNA fragment was cut and isolated that contained the DNA mutation Gln^{12}->Glu^{12}. From the 509 base pair double stranded DNA product obtained after DNA amplification "B", a 197 base pair HindIII to BsmI DNA fragment was cut and isolated that contained the DNA mutation Gln^{21}->Glu^{21}.

[0117] The "A" and "B" fragments were ligated together with a 4.8 kilo-base pair XbaI to BsmI DNA plasmid vector fragment. The ligation mix consisted of equal molar DNA restriction fragments, ligation buffer (25 mM Tris-HCl pH 7.8, 10 mM $MgCl_2$, 2 mM DTT, 0.5 mM rATP, and 100 ug/ml BSA) and T4 DNA ligase and was incubated overnight at 14°C. The ligated DNA was then transformed into E. coli FM5 cells by electroporation using a Bio Rad Gene Pulser apparatus (BioRad, Richmond, CA). A clone was isolated and the plasmid construct verified to contain the two mutations by DNA sequencing. This 'intermediate' vector also contained a deletion of a 193 base pair BsmI to BsmI DNA fragment. The final plasmid vector was constructed by ligation and transformation (as described above) of DNA fragments obtained by cutting and isolating a 2 kilo-base pair SstI to BamHI DNA fragment from the intermediate vector, a 2.8 kbp SstI to EcoRI DNA fragment from the plasmid vector, and a 360 bp BamHI to EcoRI DNA fragment from the plasmid vector. The final construct was verified by DNA sequencing the G-CSF gene. Cultures were grown, and the cells were harvested, and the G-CSF analogs were purified as set forth below.

[0118] As indicated above, any combination of mutagenesis techniques may be used to generate a G-CSF analog nucleic acid (and expression product) having one or more than one alteration. The two examples above, using M13-based mutagenesis and gene amplification-based mutagenesis, are illustrative.

E. Expression of G-CSF Analog DNA

[0119] The G-CSF analog DNAs were then placed into a plasmid vector and used to transform E. coli strain FM5 (ATCC#53911). The present G-CSF analog DNAs contained on plasmids and in bacterial host cells are available from the American Type Culture Collection, Rockville, MD, and the accession designations are indicated below.

[0120] One liter cultures were grown in broth containing 10g tryptone, 5g yeast extract and 5g NaCl) at 30°C until reaching a density at A^{600} of 0.5, at which point they were rapidly heated to 42°C. The flasks were allowed to continue shaking at for three hours.

[0121] Other prokaryotic or eukaryotic host cells may also be used, such as other bacterial cells, strains or species, mammalian cells in culture (COS, CHO or other types) insect cells or multicellular organs or organisms, or plant cells or multicellular organs or organisms, and a skilled practitioner will recognize the appropriate host. The present G-CSF analogs and related compositions may also be prepared synthetically, as, for example, by solid phase peptide synthesis methds, or other chemical manufacturing techniques. Other cloning and expression systems will be apparent to those skilled in the art.

F. Purification of G-CSF Analog Protein

[0122] Cells were harvested by centrifugation (10,000 x G, 20 minutes, 4°C). The pellet (usually 5 grams) was resuspended in 30 ml of 1mM DTT and passed three times through a French press cell at 10,000 psi. The broken cell suspension was centrifuged at 10,000g for 30 minutes, the supernatant removed, and the pellet resuspended in 30-40 ml water. This was recentrifuged at 10,000 x G for 30 minutes, and this pellet was dissolved in 25 ml of 2% Sarkosyl and 50mM Tris at pH 8. Copper sulfate was added to a concentration of 40uM, and the mixture was allowed to stir for at least 15 hours at 15-25°C. The mixture was then centrifuged at 20,000 x G for 30 minutes. The resultant solubilized protein mixture was diluted four-fold with 13.3 mM Tris, pH 7.7, the Sarkosyl was removed, and the supernatant was then applied to a DEAE-cellulose (Whatman DE-52) column equilibrated in 20mM Tris, pH 7.7. After loading and washing the column with the same buffer, the analogs were eluted with 20mM Tris /NaCl (between 35mM to 100mM depending on the analog, as indicated below), pH 7.7. For most of the analogs, the eluent from the DEAE column was adjusted to a pH of 5.4, with 50% acetic acid and diluted as necessary (to obtain the proper conductivity) with 5mM sodium acetate pH 5.4. The solution was then loaded onto a CM-sepharose column equilibrated in 20 mM sodium acetate, pH 5.4. The column was then washed with 20mM NaAc, pH 5.4 until the absorbance at 280 nm was approximately zero. The G-CSF analog was then eluted with sodium acetate/NaCl in concentrations as described below in Table 4. The DEAE column eluents for those analogs not applied to the CM-sepharose column were dialyzed directly into 10mM NaAc, ph 4.0 buffer. The purified G-CSF analogs were then suitably isolated for in vitro analysis. The salt concentrations used for eluting the analogs varied, as noted above. Below, the salt concentrations for the DEAE cellulose column and for the CM-sepharose column are listed:

Table 4

Salt Concentrations

Analog	DEAE Cellulose	CM-Sepharose
Lys^{17}->Arg^{17}	35mM	37.5mM
Lys^{24}->Arg^{24}	35mM	37.5mM
Lys^{35}->Arg^{35}	35mM	37.5mM
Lys^{41}->Arg^{41}	35mM	37.5mM
$Lys^{17,24,35}$->$Arg^{17,24,35}$	35mM	37.5mM
$Lys^{17,35,41}$->$Arg^{17,35,41}$	35mM	37.5mM

Table 4 Con't

Analog	DEAE Cellulose	CM-Sepharose
$Lys^{24,35,41}$->$Arg^{24,35,41}$	35mM	37.5mM
$Lys^{17,24,35,41}$->$Arg^{17,24,35,41}$	35mM	37.5mM
$Lys^{17,24,41}$->$Arg^{17,24,41}$	35mM	37.5mM
Gln^{68}->Glu^{68}	60mM	37.5mM
$Cys^{37,43}$->$Ser^{37,43}$	40mM	37.5mM
Gln^{26}->Ala^{26}	40mM	40mM
Gln^{174}->Ala^{174}	40mM	40mM
Arg^{170}->Ala^{170}	40mM	40mM
Arg^{167}->Ala^{167}	40mM	40mM
Deletion 167*	N/A	N/A
Lys^{41}->Ala^{41}	160mM	40mM
His^{44}->Lys^{44}	40mM	60mM
Glu^{47}->Ala^{47}	40mM	40mM
Arg^{23}->Ala^{23}	40mM	40mM
Lys^{24}->Ala^{24}	120mM	40mM
Glu^{20}->Ala^{20}	40mM	60mM
Asp^{28}->Ala^{28}	40mM	80mM
Met^{127}->Glu^{127}	80mM	40mM
Met^{138}->Glu^{138}	80mM	40mM
Met^{127}->Leu^{127}	40mM	40mM
Met^{138}->Leu^{138}	40mM	40mM
Cys^{18}->Ala^{18}	40mM	37.5mM
$Gln^{12,21}$->$Glu^{12,21}$	60mM	37.5mM
$Gln^{12,21,68}$->$Glu^{12,21,68}$ Glu^{20}->Ala^{20}; Ser^{13}->Gly^{13}	40mM	80mM

Table 4 Con't

Analog	DEAE Cellulose	CM-Sepharose
$Met^{127,138}$->$Leu^{127,138}$	40mM	40mM
Ser^{13}->Ala^{13}	40mM	40mM
Lys^{17}->Ala^{17}	80mM	40mM
Gln^{121}->Ala^{121}	40mM	60mM
Gln^{21}->Ala^{21}	50mM	Gradient 0 -150mM
His^{44}->Ala^{44}**	40mM	N/A
His^{53}->Ala^{53}**	50mM	N/A
Asp^{110}->Ala^{110}**	40mM	N/A
Asp^{113}->Ala^{113}**	40mM	N/A
Thr^{117}->Ala^{117}**	50mM	N/A
Asp^{28}->Ala^{28}; Asp^{110} Ala^{110}**	50mM	N/A
Glu^{124}->Ala^{124}**	40mM	40mM

* For Deletion ^{167}, the data are unavailable.
** For these analogs, the DEAE cellulose column alone was use for purification.

[0123] The above purification methods are illustrative, and a skilled practitioner will recognize that other means are available for obtaining the present G-CSF analogs.

G. Biological Assays

[0124] Regardless of which methods were used to create the present G-CSF analogs, the analogs were subject to assays for biological activity. Tritiated thymidine assays were conducted to ascertain the degree of cell division. Other biological assays, however, may be used to ascertain the desired activity. Biological assays such as assaying for the ability to induce terminal differentiation in mouse WEHI-3B (D+) leukemic cell line, also provides indication of G-CSF activity. See Nicola, et al., Blood 54: 614-27 (1979). Other in vitro assays may be used to ascertain biological activity. See Nicola, Annu. Rev. Biochem. 58: 45-77 (1989). In general, the test for biological activity should provide analysis for the desired result, such as increase or decrease in biological activity (as compared to non-altered G-CSF), different biological activity (as compared to non-altered G-CSF), receptor affinity analysis, or serum half-life analysis. The list is incomplete, and those skilled in the art will recognize other assays useful for testing for the desired end result.

[0125] The ^{3}H-thymidine assay was performed using standard methods. Bone marrow was obtained from sacrificed female Balb C mice. Bone marrow cells were briefly suspended, centrifuged, and resuspended in a growth medium. A 160 ul aliquot containing approximately 10,000 cells was placed into each well of a 96 well micro-titer plate. Samples of the purified G-CSF analog(as prepared above) were added to each well, and incubated for 68 hours. Tritiated thymidine was added to the wells and allowed to incubate for 5 additional hours. After the 5 hour incubation time, the cells were harvested, filtered, and thoroughly rinsed. The filters were added to a vial containing scintillation fluid. The beta emissions were counted (LKB Betaplate scintillation counter). Standards and analogs were analyzed in triplicate, and samples which fell substantially above or below the standard curve were re-assayed with the proper dilution.

The results reported here are the average of the triplicate analog data relative to the unaltered recombinant human G-CSF standard results.

H. HPLC Analysis

[0126] High pressure liquid chromatography was performed on purified samples of analog. Alth ugh peak position on a reverse phase HPLC column is not a definitive indication of structural similarity between two proteins, analogs which have similar retention times may have the same type of hydrophobic interactions with the HPLC column as the non-altered molecule. This is one indication of an overall similar structure.

[0127] Samples of the analog and the non-altered recombinant human G-CSF were analyzed on a reverse phase (0.46 x 25 cm) Vydac 214TP54 column (Separations Group, Inc. Hesperia, CA). The purified analog G-CSF samples were prepared in 20 mM acetate and 40 mM NaCl solution buffered at pH 5.2 to a final concentration of 0.1 mg/ml to 5 mg/ml, depending on how the analog performed in the column. Varying amounts (depending on the concentration) were loaded onto the HPLC column, which had been equilibrated with an aqueous solution containing 1% isopropanol, 52.8% acetonitrile, and .38% trifluoro acetate (TFA). The samples were subjected to a gradient of 0.86%/minute acetonitrile, and .002% TFA.

I. Results

[0128] Presented below are the results of the above biological assays and HPLC analysis. Biological activity is the average of triplicate data and reported as a percentage of the control standard (non-altered G-CSF). Relative HPLC peak position is the position of the analog G-CSF relative to the control standard (non-altered G-CSF) peak. The "+" or "-" symbols indicate whether the analog HPLC peak was in advance of or followed the control standard peak (in minutes). Not all of the variants had been analyzed for relative HPLC peak, and only those so analyzed are included below. Also presented are the American Type Culture Collection designations for E. coli host cells containing the nucleic acids coding for the present analogs, as prepared above.

Table 5

Seq. ID	Variant	Analog	Relative HPLC Peak	ATCC No.	% Normal G-CSF Activity
67	1	Lys^{17}->Arg^{17}	N/A	69184	N/A
68	2	Lys^{24}->Arg^{24}	N/A	69185	N/A
69	3	Lys^{35}->Arg^{35}	N/A	69186	N/A
70	4	Lys^{41}->Arg^{41}	N/A	69187	N/A
71	5	$Lys^{17,24,35}$->$Arg^{17,24,35}$	N/A	69189	N/A
72	6	$Lys^{17,35,41}$->$Arg^{17,35,41}$	N/A	69192	N/A
73	7	$Lys^{24,35,41}$->$Arg^{24,35,41}$	N/A	69191	N/A
74	8	$Lys^{17,24,35,41}$ ->$Arg^{17,24,35,41}$	N/A	69193	N/A
75	9	$Lys^{17,24,41}$->$Arg^{17,24,41}$	N/A	69190	N/A
76	10	Gln^{68}->Glu^{68}	N/A	69196	N/A
77	11	$Cys^{37,43}$->$Ser^{37,43}$	N/A	69197	N/A
78	12	Gln^{26}->Ala^{26}	+.96	69201	51%
79	13	Gln^{174}->Ala^{174}	+.14	69202	100%
80	14	Arg^{170}->Ala^{170}	+.78	69203	100%

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Table 5 Con't

Seq. ID	Variant	Analog	Relative HPLC Peak	ATCC No.	% Normal G-CSF Activity
81	15	Arg^{167}->Ala^{167}	+.54	69204	110%
82	16	Deletion 167	-.99	69207	N/A
83	17	Lys^{41}->Ala^{41}	+.25	69208	81%
84	18	His^{44}->Lys^{44}	-1.53	69212	70%
85	19	Glu^{47}->Ala^{47}	+.14	69205	0%
86	20	Arg^{23}->Ala^{23}	-.03	69206	31%
87	21	Lys^{24}->Ala^{24}	+1.95	69213	0%
88	22	Glu^{20}->Ala^{20}	-0.07	69211	0%
89	23	Asp^{28}->Ala^{28}	-.30	69210	147%
90	24	Met^{127}->Glu^{127}	N/A	69223	N/A
91	25	Met^{138}->Glu^{138}	N/A	69222	N/A
92	26	Met^{127}->Leu^{127}	N/A	69198	N/A
93	27	Met^{138}->Leu^{138}	N/A	69199	N/A
94	28	Cys^{18}->Ala^{18}	N/A	69188	N/A
95	29	$Gln^{12,21}$->$Glu^{12,21}$	N/A	69194	N/A
96	30	$Gln^{12,21,68}$->$Glu^{12,21,68}$	N/A	69195	N/A
97	31	Glu^{20}->Ala^{20}; Ser^{13}	+1.74	69209	0%

EP 0 612 846 B1

Table 5 Con't

Seq. ID	Variant	Analog	Relative HPLC Peak	ATCC No.	% Normal G-CSF Activity
		->Gly^{13}			
98	32	$Met^{127,138}$->$Leu^{127,138}$	+1.43	69200	98%
99	33	Ser^{13}->Ala^{13}	0	69221	110%
100	34	Lys^{17}->Ala^{17}	+.50	69226	70%
101	35	Gln^{121}->Ala^{121}	+2.7	69225	100%
102	36	Gln^{21}->Ala^{21}	+0.63	69217	9.6%
103	37	His^{44}->Ala^{44}	+1.52	69215	10.8%
104	38	His^{53}->Ala^{53}	+0.99	69219	8.3%
105	39	Asp^{110}->Ala^{110}	+1.97	69216	29%
106	40	Asp^{113}->Ala^{113}	-0.34	69218	0%
107	41	Thr^{117}->Ala^{117}	+0.4	69214	9.7%
108	42	Asp^{28}->Ala^{28}; Asp^{110} Ala^{110}	+3.2	69220	20.6%

Table 5 Con't

Seq. ID	Variant	Analog	Relative HPLC Peak	ATCC No.	% Normal G-CSF Activity
109	43	Glu^{124}->Ala^{124}	+0.16	69224	75%
110	44	Phe^{114}->Val^{114}, T^{117}->A^{117}**	+0.53		0%

**This analog was apparently a result of an inadvertent error in the oligo which was used to prepare number 41, above (Thr^{117}->Ala^{117}), and thus was prepared identically to the process used for that analog.

"N/A" indicates data which are not available.

1. Identification of Structure-Function Relationships

[0129] The first step used to design the present analogs was to determine what moieties are necessary for structural integrity of the G-CSF molecule. This was done at the amino acid residue level, although the atomic level is also available for analysis. Modification of the residues necessary for structural integrity results in change in the overall structure of the G-CSF molecule. This may or may not be desirable, depending on the analog one wishes to produce. The working examples here were designed to maintain the overall structural integrity of the G-CSF molecule, for the purpose of maintain G-CSF receptor binding of the analog to the G-CSF receptor (as used in this section below, the "G-CSF receptor" refers to the natural G-CSF receptor, found on hematopoietic cells). It was assumed, and confirmed by the studies presented here, that G-CSF receptor binding is a necessary step for at least one biological activity, as determined by the above biological assays.

[0130] As can be seen from the figures, G-CSF (here, recombinant human met-G-CSF) is an antiparallel 4-alpha helical bundle with a left-handed twist, and with overall dimensions of 45 Å x 30Å x 24Å. The four helices within the bundle are referred to as helices A, B, C and D, and their connecting loops are known as the AB, BC and CD loops. The helix crossing angles range from -167.5° to -159.4°. Helices A, B, and C are straight, whereas helix D contains two kinds of structural characteristics, at Gly 150 and Ser 160 (of the recombinant human met-G-CSF). Overall, the G-CSF molecule is a bundle of four helices, connected in series by external loops. This structural information was then correlated with known functional information. It was known that residues (including methionine at position 1) 47, 23, 24, 20, 21, 44, 53, 113, 110, 28 and 114 may be modified, and the effect on biological activity would be substantial.

[0131] The majority of single mutations which lowered biological activity were centered around two regions of G-CSF that are separated by 30Å, and are located on different faces of the four helix bundle. One region involves interactions between the A helix and the D helix. This is further confirmed by the presence of salt bridges in the non-altered molecule as follows:

Atom	Helix	Atom	Helix	Distance
Arg 170 N1	D	Tyr 166 OH	A	3.3
Tyr 166 OH	D	Arg 23 N2	A	3.3
Glu 163 OE1	D	Arg 23 N1	A	2.8
Arg 23 N1	A	Gln 26 OE1	A	3.1
Gln 159 NE2	D	Gln 26 O	A	3.3

[0132] Distances reported here were for molecule A, as indicated in FIGURE 5 (wherein three G-CSF molecules crystallized together and were designated as A, B, and C). As can be seen, there is a web of salt bridges between helix A and helix D, which act to stabilize the helix A structure, and therefore affect the overall structure of the G-CSF molecule.

[0133] The area centering around residues Glu 20, Arg 23 and Lys 24 are found on the hydrophilic face of the A helix (residues 20-37). Substitution of the residues with the non-charged alanine residue at positions 20 and 23 resulted in similar HPLC retention times, indicating similarity in structure. Alteration of these sites altered the biological activity (as indicated by the present assays). Substitution at Lys 24 altered biological activity, but did not result in a similar HPLC retention time as the other two alterations.

[0134] The second site at which alteration lowered biological activity involves the AB helix. Changing glutamine at position 47 to alanine (analog no. 19, above) reduced biological activity (in the thymidine uptake assay) to zero. The AB helix is predominantly hydrophobic, except at the amino and carboxy termini; it contains one turn of a 3^{10} helix. There are two histadines at each termini (His 44 and His 56) and an additional glutamate at residue 46 which has the potential to form a salt bridge to His 44. The fourier transformed infra red spectrographic analysis (FTIR) of the analog suggests this analog is structurally similar to the non-altered recombinant G-CSF molecule. Further testing showed that this analog would not crystallize under the same conditions as the non-altered recombinant molecule.

[0135] Alterations at the carboxy terminus (Gln 174, Arg 167 and Arg 170) had little effect on biological activity. In contrast, deletion of th⁻ last eight residues (167-175) lowered biological activity. These results may indicat⁻ that the deletion destabilizes the overall structure which prevents the mutant from proper binding to the G-CSF receptor (and thus initiating signal transduction).

[0136] Generally, for the G-CSF internal core -- the internal four helix bundle lacking the external loops --the hydrophobic internal residues are essential for structural integrity. For example, in helix A, the internal hydrophobic residues

are (with methionine being position 1) Phe 14, Cys 18, Val 22, Ile 25, Ile 32 and Leu 36. Generally, for the G-CSF internal core -- the internal four helix bundle lacking the external loops --the hydrophobic internal residues are essential for structural integrity. For example, in helix A, the internal hydrophobic residues are (with methionine being position 1 as in FIGURE 1) Phe 14, Cys 18, Val 22, Ile 25, Ile 32 and Leu 36. The other hydrophobic residues (again with the met at position 1) are: helix B, Ala 72, Leu 76, Leu 79, Leu 83, Tyr 86, Leu 90 Leu 93; helix C, Leu 104, Leu 107, Val 111, Ala 114, Ile 118, Met 122; and helix D, Val 154, Val 158, Phe 161, Val 164, Val 168, Leu 172.

[0137] The above biological activity data, from the presently prepared G-CSF analogs, demonstrate that modification of the external loops interfere least with G-CSF overall structure. Preferred loops for analog prepration are the AB loop and the CD loop. The loops are relatively flexible structures as compared to the helices. The loops may contribute to the proteolysis of the molecule. G-CSF is relatively fast acting in vivo as the purpose the molecule serves is to generate a response to a biological challenge, i.e., selectively stimulate neutrophils. The G-CSF turnover rate is also relatively fast. The flexibility of the loops may provide a "handle" for proteases to attach to the molecule to inactivate the molecule. Modification of the loops to prevent protease degradation, yet have (via retention of the overall structure of non-modified G-CSF) no loss in biological activity may be accomplished.

[0138] This phenomenon is probably not limited to the G-CSF molecule but may also be common to the other molecules with known similar overall structures, as presented in Figure 2. Alteration of the external loop of, for example hGH, Interferon B, IL-2, GM-CSF and IL-4 may provide the least change to the overall structure. The external loops on the GM-CSF molecule are not as flexible as those found on the G-CSF molecule, and this may indicate a longer serum life, consistent with the broader biological activity of GM-CSF. Thus, the external loops of GM-CSF may be modified by releasing the external loops from the beta-sheet structure, which may make the loops more flexible (similar to those G-CSF) and therefore make the molecule more susceptible to protease degradation (and thus increase the turnover rate).

[0139] Alteration of these external loops may be effected by stabilizing the loops by connection to one or more of the internal helices. Connecting means are known to those in the art, such as the formation of a beta sheet, salt bridge, disulfide bonding or hydrophobic interactions, and other means are available. Also, deletion of one or more moieties, such as one or more amino acid residues or portions thereof, to prepare an abbreviated molecule and thus eliminate certain portions of the external loops may be effected.

[0140] Thus, by alteration of the external loops, preferably the AB loop (amino acids 58-72 of r-hu-met G-CSF) or the CD loop (amino acids 119 to 145 of r-hu-met-G-CSF), and less preferably the amino terminus (amino acids 1-10), one may therefore modify the biological function without elimination of G-CSF receptor binding. For example, one may: (1) increase half-life (or prepare an oral dosage form, for example) of the G-CSF molecule by, for example, decreasing the ability of proteases to act on the G-CSF molecule or adding chemical modifications to the G-CSF molecule, such as one or more polyethylene glycol molecules or enteric coatings for oral formulation which would act to change some characteristic of the G-CSF molecule as described above, such as increasing serum or other half-life or decreasing antigenicity; (2) prepare a hybrid molecule, such as combining G-CSF with part or all of another protein such as another cytokine or another protein which effects signal transduction via entry through the cell through a G-CSF receptor transport mechanism; or (3) increase the biological activity as in, for example, the ability to selectively stimulate neutrophils (as compared to a non-modified G-CSF molecule). This list is not limited to the above exemplars.

[0141] Another aspect observed from the above data is that stabilizing surface interactions may affect biological activity. This is apparent from comparing analogs 23 and 40. Analog 23 contains a substitution of the charged asparagine residue at position 28 for the neutrally-charged alanine residue in that position, and such substitution resulted in a 50% increase in the biological activity (as measured by the disclosed thymidine uptake assays). The asparagine residue at position 28 has a surface interaction with the asparagine residue at position 113; both residues being negatively charged, there is a certain amount of instability (due to the repelling of like charged moieties). When, however the asparagine at position 113 is replaced with the neutrally-charged alanine, the biological activity drops to zero (in the present assay system). This indicates that the asparagine at position 113 is critical to biological activity, and elimination of the asparagine at position 28 serves to increase the effect that asparagine at position 113 possesses.

[0142] The domains required for G-CSF receptor binding were also determined based on the above analogs prepared and the G-CSF structure. The G-CSF receptor binding domain is located at residues (with methionine being position 1) 11-57 (between the A and AB helix) and 100-118 (between the B and C helices). One may also prepare abbreviated molecules capable of binding to a G-CSF receptor and initiate signal transduction for selectively stimulating neutrophils by changing the external loop structure and having the receptor binding domains remain intact.

[0143] Residues essential for biological activity and presumably G-CSF receptor binding or signal transduction have been identified. Two distinct sites are located on two different regions of the secondary structure. What is here called "Site A" is located on a helix which is constrained by salt bridge contacts betw en two other members of the helical bundle. The second site, "Site B" is located on a relatively more flexible helix, AB. The AB helix is potentially more sensitive to local pH changes because of the type and position of the residues at the carboxy and amino termini. Th functional importance of this flexible helix may be important in a conformationally induced fit when binding to the G-CSF receptor. Additionally, the extended portion of the D helix is also indicated to be a G-CSF receptor binding domain, as

ascertained by direct mutational and indirect comparative protein structure analysis. Deletion of the carboxy terminal end of r-hu-met-G-CSF reduces activity as it does for hGH, see, Cunningham and Wells, Science 244: 1081-1084 (1989). Cytokines which have similar structures, such as IL-6 and GM-CSF with predicted similar topology also center their biological activity along the carboxy end of the D helix, see Bazan, Immunology Today 11: 350-354 (1990)

[0144] A comparison of the structures and the positions of G-CSF receptor binding determinants between G-CSF and hGH suggests both molecules have similar means of signal transduction. Two separate G-CSF receptor binding sites have been identified for hGH De Vos et al., Science 255: 306-32 (1991). One of these binding sites (called "Site I") is formed by residues on the exposed faces of hGH's helix 1, the connection region between helix 1 and 2, and helix 4. The second binding site (called "Site II") is formed by surface residues of helix 1 and helix 3.

[0145] The G-CSF receptor binding determinates identified for G-CSF are located in the same relative positions as those identified for hGH. The G-CSF receptor binding site located in the connecting region between helix A and B on the AB helix (Site A) is similar in position to that reported for a small piece of helix (residues 38-47) of hGH. A single point mutation in the AB helix of G-CSF significantly reduces biological activity (as ascertained in the present assays), indicating the role in a G-CSF receptor-ligand interface. Binding of the G-CSF receptor may destabilize the 3^{10} helical nature of this region and induce a conformation change improving the binding energy of the ligand/G-CSF receptor complex.

[0146] In the hGH receptor complex, the first helix of the bundle donates residues to both of the binding sites required to dimerize the hGH receptor Mutational analysis of the corresponding helix of G-CSF (helix A) has identified three residues which are required for biological activity. Of these three residues, Glu 20 and Arg 24 lie on one face of the helical bundle towards helix C, whereas the side chain of Arg 23 (in two of the three molecules in the asymmetric unit) points to the face of the bundle towards helix D. The position of side chains of these biologically important residues indicates that similar to hGH, G-CSF may have a second G-CSF receptor binding site along the interface between helix A and helix C. In contrast with the hGH molecule, the amino terminus of G-CSF has a limited biological role as deletion of the first 11 residues has little effect on the biological activity.

[0147] As indicated above (see FIGURE 2, for example), G-CSF has a topological similarity with other cytokines. A correlation of the structure with previous biochemical studies, mutational analysis and direct comparison of specific residues of the hGH receptor complex indicates that G-CSF has two receptor binding sites. Site A lies along the interface of the A and D helices and includes residues in the small AB helix. Site B also includes residues in the A helix but lies along the interface between helices A and C. The conservation of structure and relative positions of biologically important residues between G-CSF and hGH is one indication of a common method of signal transduction in that the receptor is bound in two places. It is therefore found that G-CSF analogs possessing altered G-CSF receptor binding domains may be prepared by alteration at either of the G-CSF receptor binding sites (residues 20-57 and 145-175).

[0148] Knowledge of the three dimensional structure and correlation of the composition of G-CSF protein makes possible a systematic, rational method for preparing G-CSF analogs. The above working examples have demonstrated that the limitations of the size and polarity of the side chains within the core of the structure dictate how much change the molecule can tolerate before the overall structure is changed.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Amgen Inc.

(ii) TITLE OF INVENTION: G-CSF ANALOG COMPOSITIONS AND METHODS

(iii) NUMBER OF SEQUENCES: 110

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSSE: Amgen Inc.
(B) STREET: Amgen Center, 1840 DeHavilland Drive
(C) CITY: Thousand Oaks
(D) STATE: California
(E) COUNTRY: United States of America
(F) ZIP: 91320-1789

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 565 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 30..554

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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TCTAGAAAAA ACCAAGGAGG TAATAAATA ATG ACT CCA TTA GGT CCT GCT TCT          53
                                Met Thr Pro Leu Gly Pro Ala Ser
                                  1               5

TCT CTG CCG CAA AGC TTT CTG CTG AAA TGT CTG GAA CAG GTT CGT AAA          101
Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln Val Arg Lys
    10                  15                  20

ATC CAG GGT GAC GGT GCT GCA CTG CAA GAA AAA CTG TGC GCT ACT TAC          149
Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu Cys Ala Thr Tyr
 25                  30                  35                  40
```

```
AAA CTG TGC CAT CCG GAA GAG CTG GTA CTG CTG GGT CAT TCT CTT GGG      197
Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu Gly His Ser Leu Gly
                45                  50                  55

ATC CCG TGG GCT CCG CTG TCT TCT TGT CCA TCT CAA GCT CTT CAG CTG      245
Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro Ser Gln Ala Leu Gln Leu
            60                  65                  70

GCT GGT TGT CTG TCT CAA CTG CAT TCT GGT CTG TTC CTG TAT CAG GGT      293
Ala Gly Cys Leu Ser Gln Leu His Ser Gly Leu Phe Leu Tyr Gln Gly
        75                  80                  85

CTT CTG CAA GCT CTG GAA GGT ATC TCT CCG GAA CTG GGT CCG ACT CTG      341
Leu Leu Gln Ala Leu Glu Gly Ile Ser Pro Glu Leu Gly Pro Thr Leu
    90                  95                  100

GAC ACT CTG CAG CTA GAT GTA GCT GAC TTT GCT ACT ACT ATT TGG CAA      389
Asp Thr Leu Gln Leu Asp Val Ala Asp Phe Ala Thr Thr Ile Trp Gln
105                 110                 115                 120

CAG ATG GAA GAG CTC GGT ATG GCA CCA GCT CTG CAA CCG ACT CAA GGT      437
Gln Met Glu Glu Leu Gly Met Ala Pro Ala Leu Gln Pro Thr Gln Gly
            125                 130                 135

GCT ATG CCG GCA TTC GCT TCT GCA TTC CAG CGT CGT GCA GGA GGT GTA      485
Ala Met Pro Ala Phe Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val
        140                 145                 150

CTG GTT GCT TCT CAT CTG CAA TCT TTC CTG GAA GTA TCT TAC CGT GTT      533
Leu Val Ala Ser His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val
    155                 160                 165

CTG CGT CAT CTG GCT CAG CCG TAATAGAATT C                             565
Leu Arg His Leu Ala Gln Pro
170                 175
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(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45
```

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CATTCTGCTG CGTTGTCTGG AACA 24

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

ACAGGTTCGT CGTATCCAGG GTG 23

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CACTGCAAGA ACGTCTGTGC GCT 23

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

CGCTACTTAC CGTCTGTGCC ATC 23

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CTTTCTGCTG CGTTGTCTGG AACA 24

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

ACAGGTTCGT CGTATCCAGG GTG 23

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

CTCTGCAAGA ACGTCTGTGC GCT 23

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

CTTTCTGCTG CGTTGTCTGG AACA 24

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

ACAGGTTCGT CGTATCCAGG GTG 23

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

CGCTACTTAC CGTCTGTCCC ATC 23

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

CTTTCTGCTG CGTTGTCTGG AACA 24

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

CTGCAAGA ACGTCTGTGC GCT 23

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

CGCTACTTAC CGTCTGTGCC ATC 23

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

ACAGGTTCGT CGTATCCAGG GTG 23

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

CACTGCAAGA ACGTCTGTGC GCT 23

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

CGCTACTTAC CGTCTGTGCC ATC 23

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

CTTTCTGCTG CGTTGTCTGG AACA 24

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

AGGTTCGT CGTATCCAGG GTG 23

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

CACTGCAAGA ACGTCTGTGC GCT 23

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CGCTACTTAC CGTCTGTGCC ATC 23

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

TCTGCTGAAA GCTCTGGAAC AGG 23

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

CTTGTCCATC TGAAGCTCTT CAG 23

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

[illegible]AAACTGT CCGCTACTTA CAAACTGTCC CATCCGG 37

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

TTCGTAAAAT CGCGGGTGAC GG 22

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

TCATCTGGCT GCGCCGTAAT AG 22

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

CCGTGTTCTG GCTCATCTGG CT 22

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GAAGTATCTT ACGCTGTTCT GCGT 24

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GAAGTATCTT ACTAAGTTCT GCGTC 25

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

CTACTTAC GCACTGTGCC AT 22

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CAAACTGTGC AAGCCGGAAG AG 22

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CATCCGGAAG CACTGGTACT GC 22

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GGAACAGGTT GCTAAAATCC AGG 23

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

GAACAGGTTC GTGCGATCCA GGGTG 25

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

CAATGTCTG GCACAGGTTC GT 22

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

TCCAGGGTGC CGGTGCTGC 19

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

AAGAGCTCGG TGAGGCACCA GCT 23

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

CTCAAGGTGC TGAGCCGGCA TTC 23

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

GAGCTCGGTC TGGCACCAGC 20

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

TCAAGGTGCT CTGCCGGCAT T 21

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

TGCCGCAA GCCTTTCTGC TGA 23

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

CTTTCTGCTG GCATGTCTGG AACA 24

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

CTATTTGGCA AGCGATGGAA GAGC 24

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

CAGATGGAAG CGCTCGGTAT G 21

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

GAGCTCGGTC TGGCACCAGC 20

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

AAGGTGCT CTGCCGGCAT T 21

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

GAAATGTCTG GCACAGGTTC GT 22

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

TTCCGGAGCG CACAGTTTG 19

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

CGAGAAGGCC TCGGGTGTCA AAC 23

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

ATGCCAAATT GCAGTAGCAA AG 22

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

ACAACGGTTT AACGTCATCG TTTC 24

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

TCAGCTACT GCTAGCTGCA GA 22

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

TCAGTCGATG ACGATCGACG TCT 23

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

TTACGAACCG CTTCCAGACA TT 22

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

TAAAATGCTT GGCGAAGGTC TGTAA 25

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

GTAGCAAATG CAGCTACATC TA 22

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

CTCATCGTT TACGTCGATG TAGAT 25

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

CCAAGAGAAG CACCCAGCAG 20

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

AGGGTTCTCT TCGTGGGTCG TC 22

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

CACTGGCGGT GATAATGAGC 20

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

CTAGGCCAGG CATTACTGG 19

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

CCACTGGCGG TGATACTGAG C 21

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

AGCAGAAAGC TTTCCGGCAG AGAAGAAGCA GGA 33

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

GCCGCAAAGC TTTCTGCTGA AATGTCTGGA AGAGGTTCGT AAAATCCAGG GTGA 54

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 59 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

CTGGAATGCA GAAGCAAATG CCGGCATAGC ACCTTCAGTC GGTTGCAGAG CTGGTGCCA 59

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Arg Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30
```

```
Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
            35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
        50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Arg Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95
```

```
Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
                100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1                 5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160
```

```
Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Arg Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Arg Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Arg Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Arg Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Arg Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
        35                  40                  45
```

```
Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
     50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                 85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Leu Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Arg Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Arg Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110
```

```
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Arg Cys Leu Glu Gln Val Arg Arg Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Arg Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15
Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Glu Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Leu Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Ser Ala Thr Tyr Lys Leu Ser His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

. r Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Ala Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60
```

```
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Xle Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1               5                  10                  15

Xxx Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125
```

```
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Ala Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Ala His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Ala Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

...r Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
        100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
    115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Val Leu Arg His Leu Ala Gln Pro
                165                 170                 174
```

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Ala Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60
```

```
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Ile Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1               5                  10                  15

Tyr Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys Lys Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125
```

```
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Ala Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Ala Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Ala Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Ala Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60
```

```
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Leu Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Ile Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Ala Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125
```

```
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:90:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Glu Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Glu Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Leu Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60
```

```
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Leu Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Val Ala Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125
```

```
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Glu Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Glu Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Glu Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Glu Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Glu Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Glu Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Gly Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Ala Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45
```

```
Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
     50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                 85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Leu Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Leu Pro Ala Phe Ala Ser Ala
    130                 135                 140

Leu Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ala Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110
```

```
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Ala Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Ala Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Ala Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys Ala Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60
```

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

Ser Gly Leu Phe Leu Tyr Gln Gly L u Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
130 135 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145 150 155 160

[illegible]e Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
165 170 175

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
1 5 10 15

[illegible]s Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
20 25 30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
35 40 45

Val Leu Leu Gly Ala Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
50 55 60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65 70 75 80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
85 90 95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
100 105 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
115 120 125

```
Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Thr Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Ala Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Ala Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Phe Ala Thr Ala Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Ala Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60
```

```
Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
 65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Ala Val Ala
            100                 105                 110

Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
        115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
    130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
 1               5                  10                  15

Xaa Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110
```

```
Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Ala Leu Gly Met Ala
          115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
      130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                    165                 170                 175
```

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 175 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

```
Met Thr Pro Leu Gly Pro Ala Ser Ser Leu Pro Gln Ser Phe Leu Leu
  1               5                  10                  15

Lys Cys Leu Glu Gln Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu
            20                  25                  30

Gln Glu Lys Leu Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu
        35                  40                  45

Val Leu Leu Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser
    50                  55                  60

Cys Pro Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His
65                  70                  75                  80

Ser Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
                85                  90                  95

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val Ala
            100                 105                 110

Asp Val Ala Thr Ala Ile Trp Gln Gln Met Glu Glu Leu Gly Met Ala
          115                 120                 125

Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe Ala Ser Ala
      130                 135                 140

Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser His Leu Gln Ser
145                 150                 155                 160

Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His Leu Ala Gln Pro
                    165                 170                 175
```

Claims

1. A method for preparing a G-CSF analog comprising the steps of:

   (a) viewing at the amino acid or atomic level information conveying the three dimensional structure of a G-CSF molecule as set forth in Figure 5;
   (b) selecting from said viewed information at least one site on said G-CSF molecule for alteration;
   (c) preparing a G-CSF molecule having such alteration; and
   (d) optionally, testing such G-CSF molecule for a desired characteristic.

2. A method for preparing a G-CSF analog according to claim 1 based on the use of a computer comprising the steps of:

   (a) providing computer expression at the amino acid or atomic level of the three dimensional structure of a G-CSF molecule as set forth in Figure 5;
   (b) selecting from said computer expression at least one site on said G-CSF molecule for alteration;
   (c) preparing a G-CSF molecule having such alteration; and,
   (d) optionally, testing such G-CSF molecule for a desired characteristic.

3. A method for preparing a G-CSF analog according to claim 2 comprising:

   (a) providing said computer with the means for displaying the three dimensional structure of a G-CSF molecule as set forth in Figure 5; including displaying the composition of moieties of said G-CSF molecule, preferably displaying the three dimensional location of each amino acid, and more preferably displaying the three dimensional location of each atom of a G-CSF molecule;
   (b) viewing said display;
   (c) selecting a site on said display for alteration in the composition of said molecule or the location of a moiety; and
   (d) preparing a G-CSF analog with such alteration.

4. A computer-based method for preparing a G-CSF analog comprising the steps of:

   (a) viewing at the amino acid or atomic level the three dimensional structure of a G-CSF molecule as set forth in Figure 5; via a computer, said computer having been previously programmed (i) to express the coordinates of a G-CSF molecule in three dimensional space, and (ii) to allow for entry of information for alteration of said G-CSF expression and viewing thereof;
   (b) selecting a site on said visual image of said G-CSF molecule for alteration;
   (c) entering information for said alteration on said computer;
   (d) viewing a three dimensional structure of said altered G-CSF molecule via said computer;
   (e) optionally repeating steps (a)-(e) above;
   (f) preparing a G-CSF analog with said alteration; and
   (g) optionally testing said G-CSF analog for a desired characteristic.

Patentansprüche

1. Verfahren zur Herstellung eines G-CSF-Analogs, welches die Schritte umfaßt:

   (a) Betrachten, auf dem Aminosäure- oder Atomniveau, von Information, welche die dreidimensionale Struktur eines G-CSF-Moleküls, wie angegeben in Fig. 5, vermittelt;

   (b) Auswählen, aus besagter betrachteten Information, von wenigstens einer Stelle auf besagtem G-CSF-Molekül für eine Veränderung;

   (c) Herstellen eines G-CSF-Moleküls mit einer solchen Veränderung; und

   (d) fakultativ, Testen eines solchen G-CSF-Moleküls auf eine gewünschte Eigenschaft.

2. Verfahren zur Herstellung eines G-CSF-Analogs nach Anspruch 1, auf der Basis der Verwendung eines Compu-

ters, welches die Schritte umfaßt:

(a) Bereitstellen einer Computerdarstellung, auf dem Aminosäure- oder Atomniveau, der dreidimensionalen Struktur eines G-CSF-Moleküls, wie angegeben in Fig. 5;

(b) Auswählen, aus besagter Computerdarstellung, von wenigstens einer Stelle auf besagtem G-CSF-Molekül für eine Veränderung;

(c) Herstellen eines G-CSF-Moleküls mit einer solchen Veränderung; und

(d) fakultativ, Testen eines solchen G-CSF-Moleküls auf eine gewünschte Eigenschaft.

3. Verfahren zur Herstellung eines G-CSF-Analogs nach Anspruch 2, welches umfaßt:

(a) Versehen besagten Computers mit Mitteln zum Anzeigen der dreidimensionalen Struktur eines G-CSF-Moleküls, wie angegeben in Fig. 5, einschließlich Anzeigen der Zusammensetzung der Einheiten besagten G-CSF-Moleküls, vorzugsweise Anzeigen der dreidimensionalen Anordnung jeder Aminosäure und bevorzugter Anzeigen der dreidimensionalen Anordnung jedes Atoms eines G-CSF-Moleküls;

(b) Betrachten besagter Ansicht;

(c) Auswählen einer Stelle auf besagter Ansicht für eine Veränderung in der Zusammensetzung besagten Moleküls oder der Anordnung einer Einheit; und

(d) Herstellen eines G-CSF-Analogs mit solch einer Änderung.

4. Computergestütztes Verfahren zur Herstellung eines G-CSF-Analogs, welches die Schritte umfaßt:

(a) Betrachten, auf dem Aminosäure- oder Atomniveau, der dreidimensionalen Struktur eines G-CSF-Moleküls, wie angegeben in Fig. 5, über einen Computer, wobei besagter Computer zuvor so programmiert worden ist, daß er (i) die Koordinaten eines G-CSF-Moleküls im dreidimensionalen Raum darstellt und (ii) die Eingabe von Information zur Veränderung besagter G-CSF-Darstellung und Betrachtung derselben ermöglicht;

(b) Auswählen einer Stelle auf besagtem visuellen Bild besagten G-CSF-Moleküls für eine Veränderung;

(c) Eingeben der Information für besagte Veränderung in besagten Computer;

(d) Betrachten einer dreidimensionalen Struktur besagten veränderten G-CSF-Moleküls über besagten Computer;

(e) fakultativ, Wiederholen der Schritte (a) - (e) oben;

(f) Herstellen eines G-CSF-Analogs mit besagter Veränderung; und

(g) fakultativ, Testen besagten G-CSF-Analogs auf eine gewünschte Eigenschaft.

Revendications

1. Procédé pour préparer un analogue de G-CSF, comprenant les étapes de :

(a) visualiser au niveau atomique ou des acides aminés des informations fournissant la structure tridimensionnelle d'une molécule de G-CSF comme indiqué sur la figure 5,
(b) choisir à partir desdites informations visualisées au moins un site sur ladite molécule de G-CSF pour altération ;
(c) préparer une molécule de G-CSF ayant une telle altération ; et
(d) éventuellement, tester une telle molécule de G-CSF en ce qui concerne une caractéristique souhaitée.

2. Procédé pour préparer un analogue de G-CSF selon la revendication 1, basé sur l'utilisation d'un ordinateur, com-

prenant les étapes de :

(a) fournir l'expression par ordinateur au niveau atomique ou des acides aminés de la structure tridimensionnelle d'une molécule de G-CSF comme indiqué sur la figure 5,
(b) choisir à partir de ladite expression par ordinateur au moins un site sur ladite molécule de G-CSF pour altération ;
(c) préparer une molécule de G-CSF ayant une telle altération ; et
(d) éventuellement, tester une telle molécule de G-CSF en ce qui concerne une caractéristique souhaitée.

3. Procédé pour préparer un analogue de G-CSF selon la revendication 2, comprenant :

(a) munir ledit ordinateur des moyens pour afficher la structure tridimensionnelle d'une molécule de G-CSF comme indiqué sur la figure 5 incluant l'affichage de la composition des fractions de ladite molécule de G-CSF, en affichant de préférence l'emplacement tridimensionnel de chaque acide aminé, et, plus préférablement, en affichant l'emplacement tridimensionnel de chaque atome d'une molécule de G-CSF ;
(b) visualiser ledit affichage ;
(c) choisir un site sur ledit affichage pour altération de la composition de ladite molécule ou de l'emplacement d'une fraction ; et
(d) préparer un analogue de G-CSF ayant une telle altération.

4. Procédé assisté par ordinateur pour préparer un analogue de G-CSF, comprenant les étapes de :

(a) visualiser au niveau atomique ou des acides aminés la structure tridimensionnelle d'une molécule de G-CSF comme indiqué sur la figure 5 via un ordinateur, ledit ordinateur ayant été préalablement programmé (i) pour exprimer les coordonnées d'une molécule de G-CSF dans l'espace tridimensionnel, et (ii) pour permettre l'entrée des informations pour l'altération de ladite expression de G-CSF et sa visualisation ;
(b) choisir un site sur ladite image visuelle de ladite molécule de G-CSF pour altération ;
(c) entrer des informations pour ladite altération dans ledit ordinateur ;
(d) visualiser une structure tridimensionnelle de ladite molécule de G-CSF altérée via ledit ordinateur ;
(e) répéter éventuellement les étapes (a) - (e) ci-dessus ;
(f) préparer un analogue de G-CSF ayant ladite altération ; et
(g) tester éventuellement ledit analogue de G-CSF en ce qui concerne une caractéristique souhaitée.

```
                                        Met Thr Pro Leu Gly Pro Ala
TCTAGAAAAAACCAAGGAGGTAATAAATA ATG ACT CCA TTA GGT CCT GCT

Ser Ser Leu Pro Gln Ser Phe Leu Leu Lys Cys Leu Glu Gln
TCT TCT CTG CCG CAA AGC TTT CTG CTG AAA TGT CTG GAA CAG

Val Arg Lys Ile Gln Gly Asp Gly Ala Ala Leu Gln Glu Lys Leu
GTT CGT AAA ATC CAG GGT GAC GGT GCT GCA CTG CAA GAA AAA CTG

Cys Ala Thr Tyr Lys Leu Cys His Pro Glu Glu Leu Val Leu Leu
TGC GCT ACT TAC AAA CTG TGC CAT CCG GAA GAG CTG GTA CTG CTG

Gly His Ser Leu Gly Ile Pro Trp Ala Pro Leu Ser Ser Cys Pro
GGT CAT TCT CTT GGG ATC CCG TGG GCT CCG CTG TCT TCT TGT CCA

Ser Gln Ala Leu Gln Leu Ala Gly Cys Leu Ser Gln Leu His Ser
TCT CAA GCT CTT CAG CTG GCT GGT TGT CTG TCT CAA CTG CAT TCT

Gly Leu Phe Leu Tyr Gln Gly Leu Leu Gln Ala Leu Glu Gly Ile
GGT CTG TTC CTG TAT CAG GGT CTT CTG CAA GCT CTG GAA GGT ATC

Ser Pro Glu Leu Gly Pro Thr Leu Asp Thr Leu Gln Leu Asp Val
TCT CCG GAA CTG GGT CCG ACT CTG GAC ACT CTG CAG CTA GAT GTA

Ala Asp Phe Ala Thr Thr Ile Trp Gln Gln Met Glu Glu Leu Gly
GCT GAC TTT GCT ACT ACT ATT TGG CAA CAG ATG GAA GAG CTC GGT

Met Ala Pro Ala Leu Gln Pro Thr Gln Gly Ala Met Pro Ala Phe
ATG GCA CCA GCT CTG CAA CCG ACT CAA GGT GCT ATG CCG GCA TTC

Ala Ser Ala Phe Gln Arg Arg Ala Gly Gly Val Leu Val Ala Ser
GCT TCT GCA TTC CAG CGT CGT GCA GGA GGT GTA CTG GTT GCT TCT

His Leu Gln Ser Phe Leu Glu Val Ser Tyr Arg Val Leu Arg His
CAT CTG CAA TCT TTC CTG GAA GTA TCT TAC CGT GTT CTG CGT CAT

Leu Ala Gln Pro OC  AM
CTG GCT CAG CCG TAA TAG AATTC
```

FIGURE 1

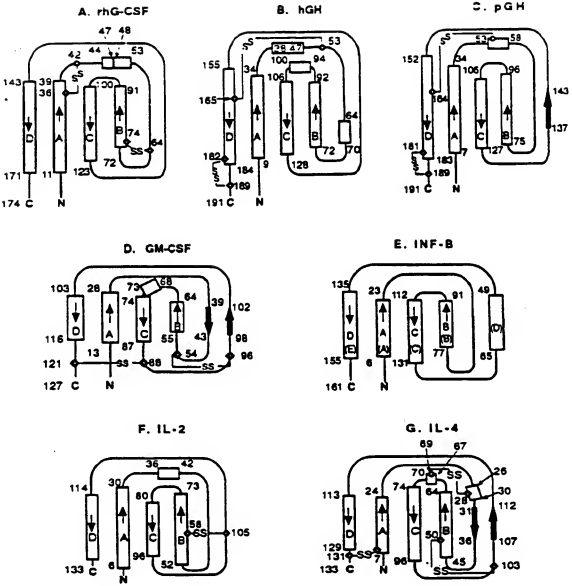

FIGURE 2

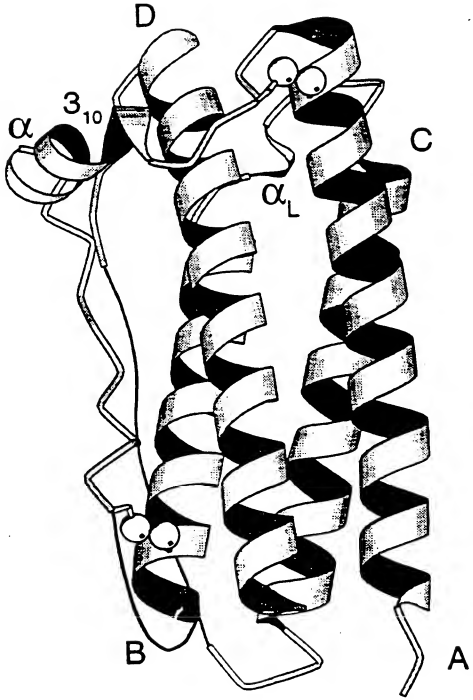

FIGURE 3

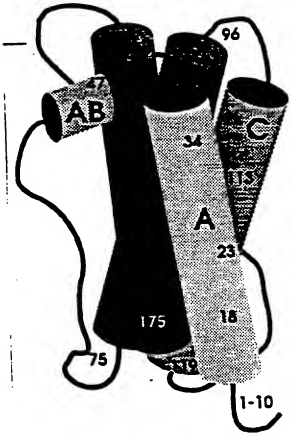

FIGURE 4

FIGURE 5

ATOM	1	CB	LEU	10	58.751	58.191	-14.868	1.00	61.22	A1
ATOM	2	CG	LEU	10	58.360	59.271	-13.939	1.00	60.19	A1
ATOM	3	CD1	LEU	10	59.307	60.461	-14.022	1.00	60.14	A1
ATOM	4	CD2	LEU	10	56.954	59.658	-14.335	1.00	60.68	A1
ATOM	5	C	LEU	10	60.544	56.734	-13.849	1.00	62.85	A1
ATOM	6	O	LEU	10	60.079	55.595	-14.041	1.00	63.08	A1
ATOM	7	HT1	LEU	10	59.876	56.135	-15.998	1.00	0.00	A1
ATOM	8	HT2	LEU	10	61.323	56.887	-16.434	1.00	0.00	A1
ATOM	9	N	LEU	10	60.328	57.059	-16.204	1.00	62.24	A1
ATOM	10	HT3	LEU	10	59.817	57.535	-16.971	1.00	0.00	A1
ATOM	11	CA	LEU	10	60.183	57.758	-14.941	1.00	62.58	A1
ATOM	12	N	PRO	11	61.357	56.962	-12.780	1.00	61.96	A1
ATOM	13	CD	PRO	11	61.960	58.238	-12.383	1.00	61.21	A1
ATOM	14	CA	PRO	11	61.832	55.889	-11.906	1.00	61.34	A1
ATOM	15	CB	PRO	11	62.915	56.547	-11.043	1.00	59.77	A1
ATOM	16	CG	PRO	11	62.511	57.983	-10.975	1.00	59.16	A1
ATOM	17	C	PRO	11	60.712	55.225	-11.109	1.00	60.68	A1
ATOM	18	O	PRO	11	60.075	55.843	-10.250	1.00	61.73	A1
ATOM	19	N	GLN	12	60.466	53.946	-11.407	1.00	59.31	A1
ATOM	20	H	GLN	12	60.944	53.573	-12.175	1.00	0.00	A1
ATOM	21	CA	GLN	12	59.468	53.121	-10.743	1.00	57.22	A1
ATOM	22	CB	GLN	12	59.779	51.646	-10.970	1.00	59.27	A1
ATOM	23	CG	GLN	12	58.620	50.714	-10.591	1.00	59.70	A1
ATOM	24	CD	GLN	12	57.604	50.575	-11.702	1.00	61.71	A1
ATOM	25	OE1	GLN	12	57.170	49.465	-11.970	1.00	65.82	A1
ATOM	26	NE2	GLN	12	57.227	51.534	-12.541	1.00	63.02	A1
ATOM	27	HE21	GLN	12	57.639	52.419	-12.489	1.00	0.00	A1
ATOM	28	HE22	GLN	12	56.500	51.308	-13.156	1.00	0.00	A1
ATOM	29	C	GLN	12	59.336	53.347	-9.245	1.00	55.34	A1
ATOM	30	O	GLN	12	58.242	53.196	-8.708	1.00	54.56	A1
ATOM	31	N	SER	13	60.423	53.732	-8.576	1.00	53.44	A1
ATOM	32	H	SER	13	61.276	53.839	-9.033	1.00	0.00	A1
ATOM	33	CA	SER	13	60.335	53.974	-7.168	1.00	52.86	A1
ATOM	34	CB	SER	13	61.704	54.144	-6.626	1.00	52.24	A1
ATOM	35	OG	SER	13	61.702	53.493	-5.362	1.00	56.64	A1
ATOM	36	HG	SER	13	61.534	52.551	-5.477	1.00	0.00	A1
ATOM	37	C	SER	13	59.497	55.214	-6.900	1.00	52.58	A1
ATOM	38	O	SER	13	58.509	55.144	-6.160	1.00	53.55	A1
ATOM	39	N	PHE	14	59.791	56.333	-7.577	1.00	50.84	A1
ATOM	40	H	PHE	14	60.469	56.292	-8.279	1.00	0.00	A1
ATOM	41	CA	PHE	14	59.067	57.590	-7.423	1.00	47.21	A1
ATOM	42	CB	PHE	14	59.611	58.590	-8.454	1.00	44.68	A1
ATOM	43	CG	PHE	14	58.618	59.669	-8.866	1.00	42.88	A1
ATOM	44	CD1	PHE	14	58.052	59.594	-10.123	1.00	40.40	A1
ATOM	45	CD2	PHE	14	58.264	60.673	-7.978	1.00	40.30	A1
ATOM	46	CE1	PHE	14	57.114	60.518	-10.507	1.00	39.59	A1
ATOM	47	CE2	PHE	14	57.329	61.587	-8.380	1.00	41.82	A1
ATOM	48	CZ	PHE	14	56.751	61.515	-9.635	1.00	41.56	A1
ATOM	49	C	PHE	14	57.605	57.263	-7.661	1.00	45.83	A1
ATOM	50	O	PHE	14	56.789	57.588	-6.805	1.00	40.07	A1
ATOM	51	N	LEU	15	57.298	56.509	-8.718	1.00	44.64	A1
ATOM	52	H	LEU	15	58.024	56.383	-9.287	1.00	0.00	A1
ATOM	53	CA	LEU	15	55.940	56.181	-9.038	1.00	44.53	A1
ATOM	54	CB	LEU	15	55.858	55.402	-10.300	1.00	48.74	A1
ATOM	55	CG	LEU	15	54.853	56.013	-11.289	1.00	51.65	A1
ATOM	56	CD1	LEU	15	55.525	57.121	-12.105	1.00	50.33	A1
ATOM	57	CD2	LEU	15	54.320	54.906	-12.204	1.00	53.77	A1
ATOM	58	C	LEU	15	55.169	55.410	-8.014	1.00	44.07	A1
ATOM	59	O	LEU	15	53.945	55.567	-7.959	1.00	45.46	A1
ATOM	60	N	LEU	16	55.809	54.620	-7.166	1.00	43.18	A1
ATOM	61	H	LEU	16	56.781	54.503	-7.251	1.00	0.00	A1
ATOM	62	CA	LEU	16	55.110	53.913	-6.095	1.00	42.96	A1
ATOM	63	CB	LEU	16	55.866	52.623	-5.751	1.00	33.34	A1
ATOM	64	CG	LEU	16	55.840	51.608	-6.868	1.00	42.25	A1
ATOM	65	CD1	LEU	16	56.889	50.567	-6.596	1.00	43.68	A1
ATOM	66	CD2	LEU	16	54.413	51.068	-7.030	1.00	42.75	A1
ATOM	67	C	LEU	16	54.963	54.778	-4.852	1.00	42.15	A1
ATOM	68	O	LEU	16	54.077	54.579	-4.018	1.00	42.65	A1
ATOM	69	N	LYS	17	55.624	55.779	-4.703	1.00	42.47	A1
ATOM	70	H	LYS	17	56.587	55.840	-5.320	1.00	0.00	A1
ATOM	71	CA	LYS	17	55.681	56.767	-3.630	1.00	42.07	A1
ATOM	72	CB	LYS	17	56.995	57.554	-3.573	1.00	44.14	A1
ATOM	73	CG	LYS	17	57.214	58.197	-2.223	1.00	49.61	A1
ATOM	74	CD	LYS	17	57.114	57.164	-1.086	1.00	55.15	A1
ATOM	75	CE	LYS	17	56.747	57.804	0.293	1.00	62.05	A1
ATOM	76	NZ	LYS	17	55.462	58.533	0.331	1.00	65.43	A1
ATOM	77	HZ1	LYS	17	54.684	57.884	0.098	1.00	0.00	A1
ATOM	78	HZ2	LYS	17	55.482	59.308	-0.362	1.00	0.00	A1
ATOM	79	HZ3	LYS	17	55.312	58.926	1.282	1.00	0.00	A1
ATOM	80	C	LYS	17	54.463	57.640	-4.051	1.00	41.20	A1
ATOM	81	O	LYS	17	53.648	57.999	-3.186	1.00	40.66	A1
ATOM	82	N	CYS	18	54.272	57.992	-5.346	1.00	39.13	A1
ATOM	83	H	CYS	18	54.998	57.809	-5.981	1.00	0.00	A1
ATOM	84	CA	CYS	18	53.080	58.656	-5.802	1.00	37.42	A1
ATOM	85	CB	CYS	18	53.092	58.891	-7.261	1.00	35.02	A1
ATOM	86	SG	CYS	18	54.421	60.026	-7.681	1.00	40.40	A1
ATOM	87	C	CYS	18	51.859	57.789	-5.502	1.00	39.33	A1
ATOM	88	O	CYS	18	50.959	58.346	-4.847	1.00	40.83	A1
ATOM	89	N	LEU	19	51.738	56.475	-5.842	1.00	37.15	A1
ATOM	90	H	LEU	19	52.462	56.038	-6.341	1.00	0.00	A1
ATOM	91	CA	LEU	19	50.521	55.702	-5.534	1.00	36.10	A1
ATOM	92	CB	LEU	19	50.644	54.204	-5.947	1.00	38.31	A1
ATOM	93	CG	LEU	19	49.410	53.271	-5.657	1.00	40.86	A1
ATOM	94	CD1	LEU	19	48.208	53.684	-6.467	1.00	39.71	A1
ATOM	95	CD2	LEU	19	49.692	51.833	-6.113	1.00	45.71	A1
ATOM	96	C	LEU	19	50.102	55.736	-4.076	1.00	33.52	A1
ATOM	97	O	LEU	19	48.930	55.949	-3.766	1.00	32.75	A1
ATOM	98	N	GLU	20	51.030	55.576	-3.166	1.00	31.88	A1
ATOM	99	H	GLU	20	51.940	55.338	-3.455	1.00	0.00	A1
ATOM	100	CA	GLU	20	50.750	55.710	-1.748	1.00	31.40	A1

FIGURE 5

```
ATOM  101 CB  GLU  20      52.053 55.334 -1.167  1.00 35.25      A1
ATOM  102 CG  GLU  20      52.508 55.504  0.260  1.00 43.21      A1
ATOM  103 CD  GLU  20      53.948 54.947  0.407  1.00 51.06      A1
ATOM  104 OE1 GLU  20      54.320 54.660  1.546  1.00 56.78      A1
ATOM  105 OE2 GLU  20      54.708 54.766 -0.570  1.00 51.57      A1
ATOM  106 C   GLU  20      50.230 57.117 -1.326  1.00 33.25      A1
ATOM  107 O   GLU  20      49.432 57.291 -0.380  1.00 33.30      A1
ATOM  108 N   GLN  21      50.660 58.167 -2.044  1.00 32.33      A1
ATOM  109 H   GLN  21      51.270 58.004 -2.794  1.00  0.00      A1
ATOM  110 CA  GLN  21      50.275 59.538 -1.742  1.00 31.00      A1
ATOM  111 CB  GLN  21      51.326 60.489 -2.340  1.00 32.37      A1
ATOM  112 CG  GLN  21      52.436 60.530 -1.272  1.00 38.01      A1
ATOM  113 CD  GLN  21      53.622 61.460 -1.504  1.00 42.67      A1
ATOM  114 OE1 GLN  21      54.008 62.236 -0.615  1.00 43.63      A1
ATOM  115 NE2 GLN  21      54.256 61.448 -2.678  1.00 42.31      A1
ATOM  116 HE21 GLN  21      53.965 60.840 -3.384  1.00  0.00      A1
ATOM  117 HE22 GLN  21      55.026 62.052 -2.730  1.00  0.00      A1
ATOM  118 C   GLN  21      48.894 59.765 -2.288  1.00 28.51      A1
ATOM  119 O   GLN  21      48.027 60.242 -1.563  1.00 28.65      A1
ATOM  120 N   VAL  22      48.682 59.319 -3.521  1.00 25.85      A1
ATOM  121 H   VAL  22      49.448 58.980 -4.013  1.00  0.00      A1
ATOM  122 CA  VAL  22      47.382 59.303 -4.161  1.00 24.94      A1
ATOM  123 CB  VAL  22      47.508 58.614 -5.526  1.00 24.09      A1
ATOM  124 CG1 VAL  22      46.154 58.378 -6.096  1.00 19.97      A1
ATOM  125 CG2 VAL  22      48.252 59.479 -6.498  1.00 25.82      A1
ATOM  126 C   VAL  22      46.418 58.549 -3.226  1.00 25.65      A1
ATOM  127 O   VAL  22      45.428 59.190 -2.800  1.00 29.31      A1
ATOM  128 N   ARG  23      46.643 57.259 -3.759  1.00 23.69      A1
ATOM  129 H   ARG  23      47.440 56.819 -3.056  1.00  0.00      A1
ATOM  130 CA  ARG  23      45.667 56.593 -1.892  1.00 20.67      A1
ATOM  131 CB  ARG  23      46.104 55.135 -1.635  1.00 20.45      A1
ATOM  132 CG  ARG  23      46.325 54.321 -2.902  1.00 17.51      A1
ATOM  133 CD  ARG  23      45.095 54.446 -3.769  1.00 21.54      A1
ATOM  134 NE  ARG  23      45.076 53.437 -4.809  1.00 24.82      A1
ATOM  135 HE  ARG  23      45.642 52.647 -4.701  1.00  0.00      A1
ATOM  136 CZ  ARG  23      44.323 53.556 -5.904  1.00 27.69      A1
ATOM  137 NH1 ARG  23      43.567 54.669 -6.006  1.00 29.51      A1
ATOM  138 HH11 ARG  23      43.562 55.377 -5.303  1.00  0.00      A1
ATOM  139 HH12 ARG  23      42.956 54.730 -6.789  1.00  0.00      A1
ATOM  140 NH2 ARG  23      44.345 52.604 -6.891  1.00 24.02      A1
ATOM  141 HH21 ARG  23      43.780 52.713 -7.709  1.00  0.00      A1
ATOM  142 HH22 ARG  23      44.936 51.802 -6.793  1.00  0.00      A1
ATOM  143 C   ARG  23      45.458 57.285 -0.560  1.00 20.56      A1
ATOM  144 O   ARG  23      44.374 57.254  0.042  1.00 20.04      A1
ATOM  145 N   LYS  24      46.485 58.015 -0.118  1.00 22.67      A1
ATOM  146 H   LYS  24      47.291 58.105 -0.668  1.00  0.00      A1
ATOM  147 CA  LYS  24      46.431 58.729  1.166  1.00 22.85      A1
ATOM  148 CB  LYS  24      47.811 59.255  1.506  1.00 26.86      A1
ATOM  149 CG  LYS  24      47.821 59.661  2.971  1.00 33.79      A1
ATOM  150 CD  LYS  24      49.121 60.265  3.404  1.00 40.73      A1
ATOM  151 CE  LYS  24      50.258 59.258  3.335  1.00 46.19      A1
ATOM  152 NZ  LYS  24      51.532 59.975  3.333  1.00 51.19      A1
ATOM  153 HZ1 LYS  24      51.627 60.498  4.225  1.00  0.00      A1
ATOM  154 HZ2 LYS  24      51.539 60.651  2.539  1.00  0.00      A1
ATOM  155 HZ3 LYS  24      52.317 59.303  3.216  1.00  0.00      A1
ATOM  156 C   LYS  24      45.455 59.893  1.101  1.00 21.66      A1
ATOM  157 O   LYS  24      44.588 60.068  1.962  1.00 20.30      A1
ATOM  158 N   ILE  25      45.549 60.696  0.044  1.00 21.66      A1
ATOM  159 H   ILE  25      46.242 60.509 -0.629  1.00  0.00      A1
ATOM  160 CA  ILE  25      44.667 61.841 -0.115  1.00 22.53      A1
ATOM  161 CB  ILE  25      45.075 62.694 -1.307  1.00 22.15      A1
ATOM  162 CG2 ILE  25      44.097 63.834 -1.439  1.00 20.44      A1
ATOM  163 CG1 ILE  25      46.475 63.230 -1.136  1.00 23.03      A1
ATOM  164 CD  ILE  25      47.188 63.281 -2.497  1.00 20.04      A1
ATOM  165 C   ILE  25      43.263 61.308 -0.352  1.00 24.75      A1
ATOM  166 O   ILE  25      42.359 61.839  0.301  1.00 26.13      A1
ATOM  167 N   GLN  26      43.065 60.289 -1.244  1.00 22.79      A1
ATOM  168 H   GLN  26      43.842 59.926 -1.726  1.00  0.00      A1
ATOM  169 CA  GLN  26      41.737 59.713 -1.437  1.00 20.12      A1
ATOM  170 CB  GLN  26      41.729 58.539 -2.341  1.00 18.99      A1
ATOM  171 CG  GLN  26      42.203 59.042 -3.627  1.00 19.77      A1
ATOM  172 CD  GLN  26      42.163 57.996 -4.684  1.00 24.26      A1
ATOM  173 OE1 GLN  26      42.550 56.853 -4.465  1.00 25.82      A1
ATOM  174 NE2 GLN  26      41.732 58.351 -5.890  1.00 27.68      A1
ATOM  175 HE21 GLN  26      41.421 59.265 -6.042  1.00  0.00      A1
ATOM  176 HE22 GLN  26      41.743 57.649 -6.552  1.00  0.00      A1
ATOM  177 C   GLN  26      41.207 59.239 -0.111  1.00 21.88      A1
ATOM  178 O   GLN  26      40.067 59.550  0.220  1.00 27.02      A1
ATOM  179 N   GLY  27      41.952 58.622  0.773  1.00 22.54      A1
ATOM  180 H   GLY  27      42.891 58.420  0.576  1.00  0.00      A1
ATOM  181 CA  GLY  27      41.386 58.191  2.037  1.00 25.55      A1
ATOM  182 C   GLY  27      40.936 59.352  2.890  1.00 27.60      A1
ATOM  183 O   GLY  27      39.889 59.251  3.526  1.00 29.95      A1
ATOM  184 N   ASP  28      41.683 60.460  2.915  1.00 29.39      A1
ATOM  185 H   ASP  28      42.547 60.454  2.448  1.00  0.00      A1
ATOM  186 CA  ASP  28      41.257 61.680  3.624  1.00 28.45      A1
ATOM  187 CB  ASP  28      42.266 62.789  3.552  1.00 30.11      A1
ATOM  188 CG  ASP  28      43.737 62.502  3.777  1.00 31.72      A1
ATOM  189 OD1 ASP  28      44.539 63.074  2.995  1.00 31.95      A1
ATOM  190 OD2 ASP  28      44.063 61.811  4.741  1.00 32.60      A1
ATOM  191 C   ASP  28      39.994 62.264  2.960  1.00 25.01      A1
ATOM  192 O   ASP  28      39.101 62.699  3.655  1.00 26.21      A1
ATOM  193 N   GLY  29      39.882 62.270  1.631  1.00 23.91      A1
ATOM  194 H   GLY  29      40.660 61.950  1.135  1.00  0.00      A1
ATOM  195 CA  GLY  29      38.729 62.694  0.886  1.00 25.69      A1
ATOM  196 C   GLY  29      37.528 61.961  1.418  1.00 27.36      A1
ATOM  197 O   GLY  29      36.648 62.558  2.061  1.00 28.14      A1
ATOM  198 N   ALA  30      37.646 60.628  1.295  1.00 27.85      A1
ATOM  199 H   ALA  30      38.442 60.288  0.844  1.00  0.00      A1
ATOM  200 CA  ALA  30      36.683 59.655  1.814  1.00 25.94      A1
ATOM  201 CB  ALA  30      37.269 58.303  1.556  1.00 22.15      A1
ATOM  202 C   ALA  30      36.356 59.842  3.308  1.00 27.18      A1
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EP 0 612 846 B1

FIGURE: 5

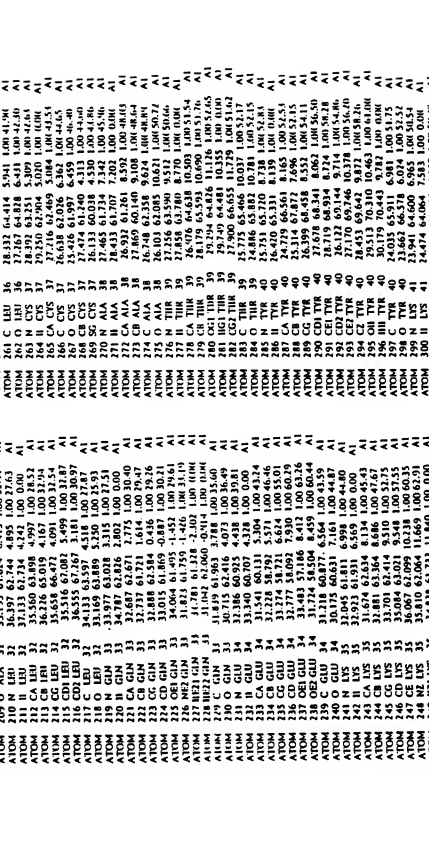

FIGURE 5

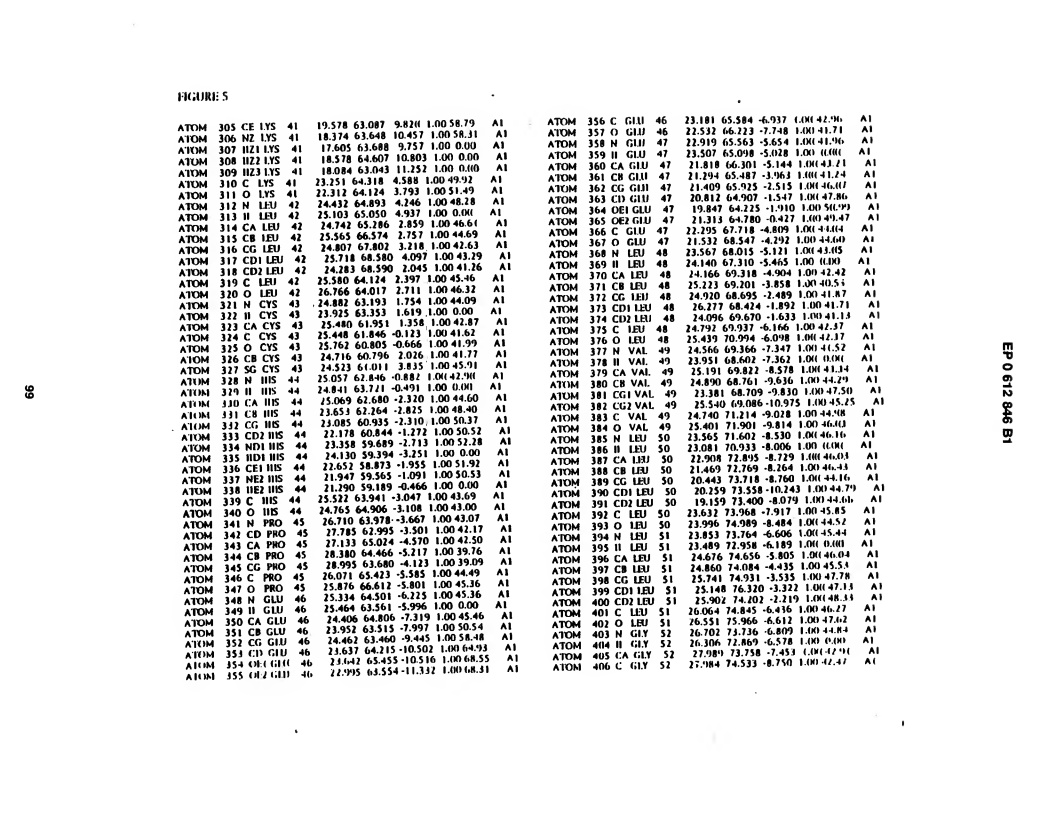

FIGURE 5

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ATOM  407 O  GLY  52   28.853  75.364 -8.983  1.00 42.06      A1
ATOM  408 N  HIS  53   27.047  74.307 -9.653  1.00 42.02      A1
ATOM  409 H  HIS  53   26.366  73.624 -9.471  1.00  0.00      A1
ATOM  410 CA HIS  53   27.009  75.104-10.861  1.00 42.23      A1
ATOM  411 CB HIS  53   25.842  74.689-11.706  1.00 42.21      A1
ATOM  412 CG HIS  53   26.076  73.399-12.460  1.00 44.60      A1
ATOM  413 CD2 HIS  53   25.112  72.774-13.200  1.00 47.49      A1
ATOM  414 ND1 HIS  53   27.180  72.669-12.578  1.00 46.76      A1
ATOM  415 HD1 HIS  53   28.039  72.853-12.139  1.00  0.00      A1
ATOM  416 CE1 HIS  53   26.954  71.641-13.346  1.00 46.90      A1
ATOM  417 NE2 HIS  53   25.704  71.725-13.707  1.00 50.22      A1
ATOM  418 HE2 HIS  53   25.237  71.033-14.239  1.00  0.00      A1
ATOM  419 C  HIS  53   26.893  76.585-10.536  1.00 42.72      A1
ATOM  420 O  HIS  53   27.622  77.399-11.068  1.00 42.03      A1
ATOM  421 N  SER  54   26.099  76.920 -9.535  1.00 45.08      A1
ATOM  422 H  SER  54   25.673  76.218 -9.001  1.00  0.00      A1
ATOM  423 CA SER  54   25.792  78.278 -9.177  1.00 46.92      A1
ATOM  424 CB SER  54   24.576  78.181 -8.289  1.00 48.86      A1
ATOM  425 OG SER  54   23.521  77.616 -9.112  1.00 53.06      A1
ATOM  426 HG SER  54   23.465  76.677 -8.918  1.00  0.00      A1
ATOM  427 C  SER  54   26.939  79.033 -8.549  1.00 47.92      A1
ATOM  428 O  SER  54   27.038  80.264 -8.655  1.00 49.60      A1
ATOM  429 N  LEU  55   27.837  78.273 -7.933  1.00 47.59      A1
ATOM  430 H  LEU  55   27.638  77.322 -7.791  1.00  0.00      A1
ATOM  431 CA LEU  55   29.075  78.810 -7.401  1.00 45.27      A1
ATOM  432 CB LEU  55   29.552  77.913 -6.243  1.00 45.49      A1
ATOM  433 CG LEU  55   28.840  77.992 -4.874  1.00 47.30      A1
ATOM  434 CD1 LEU  55   28.876  76.596 -4.299  1.00 49.52      A1
ATOM  435 CD2 LEU  55   29.530  78.921 -3.862  1.00 45.69      A1
ATOM  436 C  LEU  55   30.133  78.889 -8.492  1.00 43.63      A1
ATOM  437 O  LEU  55   31.247  79.350 -8.272  1.00 43.24      A1
ATOM  438 N  GLY  56   29.855  78.383 -9.675  1.00 41.55      A1
ATOM  439 H  GLY  56   28.984  77.959 -9.828  1.00  0.00      A1
ATOM  440 CA GLY  56   30.814  78.390-10.753  1.00 45.59      A1
ATOM  441 C  GLY  56   32.182  77.811-10.392  1.00 46.76      A1
ATOM  442 O  GLY  56   33.171  78.213-11.015  1.00 47.31      A1
ATOM  443 N  ILE  57   32.247  76.885 -9.412  1.00 47.49      A1
ATOM  444 H  ILE  57   31.392  76.594 -9.042  1.00  0.00      A1
ATOM  445 CA ILE  57   33.486  76.249 -8.950  1.00 48.28      A1
ATOM  446 CB ILE  57   33.144  75.172 -7.863  1.00 47.79      A1
ATOM  447 CG2 ILE  57   34.457  74.591 -7.348  1.00 46.85      A1
ATOM  448 CG1 ILE  57   32.338  75.764 -6.701  1.00 45.09      A1
ATOM  449 CD ILE  57   31.859  74.739 -5.659  1.00 41.23      A1
ATOM  450 C  ILE  57   34.276  75.602-10.115  1.00 49.15      A1
ATOM  451 O  ILE  57   33.678  74.935-10.968  1.00 49.04      A1
ATOM  452 N  PRO  58   35.596  75.817-10.248  1.00 49.75      A1
ATOM  453 CD PRO  58   36.402  76.743 -9.433  1.00 50.94      A1
ATOM  454 CA PRO  58   36.421  75.228-11.302  1.00 50.72      A1
ATOM  455 CB PRO  58   37.525  76.241-11.488  1.00 50.92      A1
ATOM  456 CG PRO  58   37.814  76.663-10.041  1.00 50.82      A1
ATOM  457 C  PRO  58   36.916  73.845-10.875  1.00 50.36      A1
ATOM  458 O  PRO  58   37.187  73.599 -9.691  1.00 49.75      A1
ATOM  459 N  TRP  59   37.030  72.927-11.816  1.00 50.37      A1
ATOM  460 H  TRP  59   36.888  73.141-12.760  1.00  0.00      A1
ATOM  461 CA TRP  59   37.524  71.595-11.482  1.00 51.78      A1
ATOM  462 CB TRP  59   36.435  70.562-11.857  1.00 49.06      A1
ATOM  463 CG TRP  59   35.254  70.712-10.889  1.00 46.47      A1
ATOM  464 CD2 TRP  59   35.320  70.845 -9.521  1.00 44.06      A1
ATOM  465 CE2 TRP  59   33.998  71.027 -9.205  1.00 44.18      A1
ATOM  466 CE3 TRP  59   36.274  70.842 -8.538  1.00 44.03      A1
ATOM  467 CD1 TRP  59   33.972  70.794-11.354  1.00 45.17      A1
ATOM  468 NE1 TRP  59   33.229  70.994-10.297  1.00 44.17      A1
ATOM  469 HE1 TRP  59   32.301  71.312-10.332  1.00  0.00      A1
ATOM  470 CZ2 TRP  59   33.598  71.215 -7.916  1.00 45.60      A1
ATOM  471 CZ3 TRP  59   35.893  71.028 -7.243  1.00 45.25      A1
ATOM  472 CH2 TRP  59   34.565  71.214 -6.938  1.00 46.43      A1
ATOM  473 C  TRP  59   38.815  71.435-12.256  1.00 52.84      A1
ATOM  474 O  TRP  59   38.842  71.972-13.372  1.00 54.96      A1
ATOM  475 N  ALA  60   39.912  70.834-11.777  1.00 51.97      A1
ATOM  476 H  ALA  60   39.857  70.269-10.977  1.00  0.00      A1
ATOM  477 CA ALA  60   41.108  70.870-12.609  1.00 52.18      A1
ATOM  478 CB ALA  60   42.303  70.610-11.748  1.00 51.75      A1
ATOM  479 C  ALA  60   41.055  69.857-13.746  1.00 52.16      A1
ATOM  480 O  ALA  60   40.545  68.760-13.530  1.00 52.17      A1
ATOM  481 N  PRO  61   41.435  70.145-14.986  1.00 53.34      A1
ATOM  482 CD PRO  61   41.370  71.458-15.622  1.00 54.20      A1
ATOM  483 CA PRO  61   41.691  69.145-15.995  1.00 55.57      A1
ATOM  484 CB PRO  61   41.792  69.918-17.310  1.00 54.95      A1
ATOM  485 CG PRO  61   42.211  71.297-16.901  1.00 54.05      A1
ATOM  486 C  PRO  61   42.934  68.333-15.690  1.00 57.55      A1
ATOM  487 O  PRO  61   43.757  68.664-14.834  1.00 57.20      A1
ATOM  488 N  LEU  62   43.040  67.271-16.486  1.00 59.98      A1
ATOM  489 H  LEU  62   42.285  67.067-17.077  1.00  0.00      A1
ATOM  490 CA LEU  62   44.184  66.370-16.471  1.00 63.64      A1
ATOM  491 CB LEU  62   44.062  65.417-15.260  1.00 62.72      A1
ATOM  492 CG LEU  62   45.323  64.691-14.865  1.00 64.43      A1
ATOM  493 CD1 LEU  62   46.394  65.704-14.488  1.00 64.02      A1
ATOM  494 CD2 LEU  62   45.016  63.764-13.717  1.00 64.98      A1
ATOM  495 C  LEU  62   44.214  65.611-17.812  1.00 65.60      A1
ATOM  496 OT1 LEU  62   44.256  66.302-18.844  1.00 68.47      A1
ATOM  497 OT2 LEU  62   44.194  64.371-17.845  1.00 66.57      A1
ATOM  498 CB LEU  72   57.448  63.159-19.422  1.00 63.34      A2
ATOM  499 CG LEU  72   57.716  62.495-18.117  1.00 63.40      A2
ATOM  500 CD1 LEU  72   56.719  61.408-17.913  1.00 61.50      A2
ATOM  501 CD2 LEU  72   59.107  61.901-18.121  1.00 64.22      A2
ATOM  502 C  LEU  72   55.897  65.084-18.876  1.00 65.40      A2
ATOM  503 O  LEU  72   54.827  65.301-18.316  1.00 67.10      A2
ATOM  504 HT1 LEU  72   56.469  64.683-21.261  1.00  0.00      A2
ATOM  505 HT2 LEU  72   54.827  64.355-20.951  1.00  0.00      A2
ATOM  506 N  LEU  72   55.795  63.983-20.899  1.00 66.49      A2
ATOM  507 HT3 LEU  72   55.866  63.098-21.449  1.00  0.00      A2
ATOM  508 CA LEU  72   56.064  63.714-19.512  1.00 64.91      A2
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FIGURE 5

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ATOM  509 N  ALA  73   56.807  66.046 -19.086  1.00 64.54      A2
ATOM  510 H  ALA  73   57.690  65.804 -19.432  1.00  0.00      A2
ATOM  511 CA ALA  73   56.707  67.433 -18.615  1.00 62.55      A2
ATOM  512 CB ALA  73   57.553  68.314 -19.529  1.00 64.84      A2
ATOM  513 C  ALA  73   55.219  68.024 -18.539  1.00 60.37      A2
ATOM  514 O  ALA  73   54.801  68.180 -17.456  1.00 59.42      A2
ATOM  515 N  GLY  74   54.693  68.226 -19.691  1.00 59.72      A2
ATOM  516 H  GLY  74   55.212  68.174 -20.514  1.00  0.00      A2
ATOM  517 CA GLY  74   53.336  68.728 -19.816  1.00 59.99      A2
ATOM  518 C  GLY  74   52.327  68.116 -18.865  1.00 60.27      A2
ATOM  519 O  GLY  74   51.880  68.796 -17.935  1.00 60.80      A2
ATOM  520 N  CYS  75   51.945  66.850 -19.030  1.00 59.60      A2
ATOM  521 H  CYS  75   52.160  66.358 -19.839  1.00  0.00      A2
ATOM  522 CA CYS  75   51.002  66.776 -18.078  1.00 60.17      A2
ATOM  523 CB CYS  75   50.670  64.801 -18.464  1.00 64.08      A2
ATOM  524 SG CYS  75   49.832  64.732 -20.096  1.00 73.47      A2
ATOM  525 C  CYS  75   51.502  66.346 -16.642  1.00 56.73      A2
ATOM  526 O  CYS  75   50.734  66.748 -15.765  1.00 55.82      A2
ATOM  527 N  LEU  76   52.795  66.142 -16.396  1.00 53.93      A2
ATOM  528 H  LEU  76   53.423  66.043 -17.137  1.00  0.00      A2
ATOM  529 CA LEU  76   53.325  66.156 -15.044  1.00 52.94      A2
ATOM  530 CB LEU  76   54.798  65.754 -15.181  1.00 50.81      A2
ATOM  531 CG LEU  76   55.575  65.011 -14.090  1.00 49.02      A2
ATOM  532 CD1 LEU  76   54.852  63.740 -13.698  1.00 46.76      A2
ATOM  533 CD2 LEU  76   56.951  64.633 -14.623  1.00 47.67      A2
ATOM  534 C  LEU  76   53.093  67.545 -14.425  1.00 53.65      A2
ATOM  535 O  LEU  76   52.731  67.716 -13.244  1.00 53.50      A2
ATOM  536 N  SER  77   53.137  68.553 -15.301  1.00 53.91      A2
ATOM  537 H  SER  77   53.322  68.361 -16.242  1.00  0.00      A2
ATOM  538 CA SER  77   52.882  69.932 -14.942  1.00 54.93      A2
ATOM  539 CB SER  77   53.425  70.835 -16.040  1.00 58.32      A2
ATOM  540 OG SER  77   54.806  70.587 -16.310  1.00 63.35      A2
ATOM  541 HG SER  77   54.949  69.637 -16.315  1.00  0.00      A2
ATOM  542 C  SER  77   51.382  70.172 -14.759  1.00 53.47      A2
ATOM  543 O  SER  77   50.982  70.965 -13.899  1.00 53.54      A2
ATOM  544 N  GLN  78   50.509  69.501 -15.512  1.00 51.82      A2
ATOM  545 H  GLN  78   50.857  68.901 -16.207  1.00  0.00      A2
ATOM  546 CA GLN  78   49.074  69.619 -15.349  1.00 50.74      A2
ATOM  547 CB GLN  78   48.402  68.877 -16.451  1.00 54.31      A2
ATOM  548 CG GLN  78   47.420  69.784 -17.160  1.00 58.59      A2
ATOM  549 CD GLN  78   46.557  68.940 -18.071  1.00 62.32      A2
ATOM  550 OE1 GLN  78   47.005  68.260 -18.998  1.00 65.94      A2
ATOM  551 NE2 GLN  78   45.269  68.889 -17.800  1.00 63.17      A2
ATOM  552 HE21 GLN  78   44.973  69.327 -16.972  1.00  0.00      A2
ATOM  553 HE22 GLN  78   44.704  68.444 -18.456  1.00  0.00      A2
ATOM  554 C  GLN  78   48.591  69.065 -14.011  1.00 48.17      A2
ATOM  555 O  GLN  78   47.691  69.618 -13.368  1.00 46.31      A2
ATOM  556 N  LEU  79   49.236  67.988 -13.564  1.00 45.89      A2
ATOM  557 H  LEU  79   49.920  67.584 -14.140  1.00  0.00      A2
ATOM  558 CA LEU  79   48.919  67.359 -12.294  1.00 44.54      A2
ATOM  559 CB LEU  79   49.617  66.015 -12.259  1.00 45.06      A2
ATOM  560 CG LEU  79   49.154  64.895 -11.351  1.00 45.18      A2
ATOM  561 CD1 LEU  79   49.634  63.594 -11.957  1.00 48.06      A2
ATOM  562 CD2 LEU  79   49.766  64.986 -9.969  1.00 40.31      A2
ATOM  563 C  LEU  79   49.366  68.265 -11.170  1.00 43.49      A2
ATOM  564 O  LEU  79   48.645  68.509 -10.199  1.00 43.20      A2
ATOM  565 N  HIS  80   50.556  68.834 -11.329  1.00 43.84      A2
ATOM  566 H  HIS  80   51.115  68.548 -12.085  1.00  0.00      A2
ATOM  567 CA HIS  80   51.060  69.788 -10.360  1.00 44.79      A2
ATOM  568 CB HIS  80   52.456  70.221 -10.810  1.00 43.58      A2
ATOM  569 CG HIS  80   53.030  71.031 -9.690  1.00 43.75      A2
ATOM  570 CD2 HIS  80   53.484  70.497 -8.517  1.00 47.48      A2
ATOM  571 ND1 HIS  80   53.083  72.343 -9.367  1.00 44.24      A2
ATOM  572 HD1 HIS  80   52.842  73.004 -10.255  1.00  0.00      A2
ATOM  573 CE1 HIS  80   53.530  72.641 -8.376  1.00 44.47      A2
ATOM  574 NE2 HIS  80   53.772  71.520 -7.748  1.00 48.16      A2
ATOM  575 HE2 HIS  80   54.103  71.444 -6.824  1.00  0.00      A2
ATOM  576 C  HIS  80   50.094  70.978 -10.219  1.00 44.40      A2
ATOM  577 O  HIS  80   49.643  71.294 -9.131  1.00 44.28      A2
ATOM  578 N  SER  81   49.733  71.670 -11.309  1.00 45.13      A2
ATOM  579 H  SER  81   50.136  71.459 -12.176  1.00  0.00      A2
ATOM  580 CA SER  81   48.738  72.742 -11.296  1.00 45.41      A2
ATOM  581 CB SER  81   48.612  73.347 -12.682  1.00 45.59      A2
ATOM  582 OG SER  81   49.894  73.444 -13.292  1.00 49.27      A2
ATOM  583 HG SER  81   50.058  72.670 -13.843  1.00  0.00      A2
ATOM  584 C  SER  81   47.364  72.266 -10.856  1.00 44.85      A2
ATOM  585 O  SER  81   46.604  73.064 -10.256  1.00 46.83      A2
ATOM  586 N  GLY  82   46.946  71.010 -11.092  1.00 42.16      A2
ATOM  587 H  GLY  82   47.513  70.411 -11.614  1.00  0.00      A2
ATOM  588 CA GLY  82   45.663  70.500 -10.650  1.00 39.39      A2
ATOM  589 C  GLY  82   45.569  70.461 -9.139  1.00 39.40      A2
ATOM  590 O  GLY  82   44.542  70.843 -8.544  1.00 39.64      A2
ATOM  591 N  LEU  83   46.676  70.032 -8.571  1.00 37.57      A2
ATOM  592 H  LEU  83   47.413  69.650 -9.073  1.00  0.00      A2
ATOM  593 CA LEU  83   46.826  70.007 -7.057  1.00 38.07      A2
ATOM  594 CB LEU  83   48.133  69.202 -6.748  1.00 35.67      A2
ATOM  595 CG LEU  83   48.071  67.736 -7.225  1.00 32.54      A2
ATOM  596 CD1 LEU  83   49.442  67.145 -7.319  1.00 29.77      A2
ATOM  597 CD2 LEU  83   47.180  66.974 -6.288  1.00 26.71      A2
ATOM  598 C  LEU  83   46.836  71.386 -6.354  1.00 38.48      A2
ATOM  599 O  LEU  83   46.392  71.627 -5.219  1.00 38.05      A2
ATOM  600 N  PHE  84   47.366  72.338 -7.108  1.00 40.34      A2
ATOM  601 H  PHE  84   47.804  72.078 -7.944  1.00  0.00      A2
ATOM  602 CA PHE  84   47.414  73.703 -6.688  1.00 41.54      A2
ATOM  603 CB PHE  84   48.163  74.531 -7.693  1.00 46.88      A2
ATOM  604 CG PHE  84   48.715  75.777 -6.988  1.00 55.91      A2
ATOM  605 CD1 PHE  84   49.521  75.622 -5.849  1.00 55.41      A2
ATOM  606 CD2 PHE  84   48.396  77.053 -7.469  1.00 55.79      A2
ATOM  607 CE1 PHE  84   50.004  76.737 -5.195  1.00 57.60      A2
ATOM  608 CE2 PHE  84   48.892  78.156 -6.796  1.00 57.15      A2
ATOM  609 CZ  PHE  84   49.688  78.002 -5.667  1.00 58.14      A2
ATOM  610 C  PHE  84   45.994  74.191 -6.531  1.00 40.47      A2
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EP 0 612 846 B1

FIGURE 5

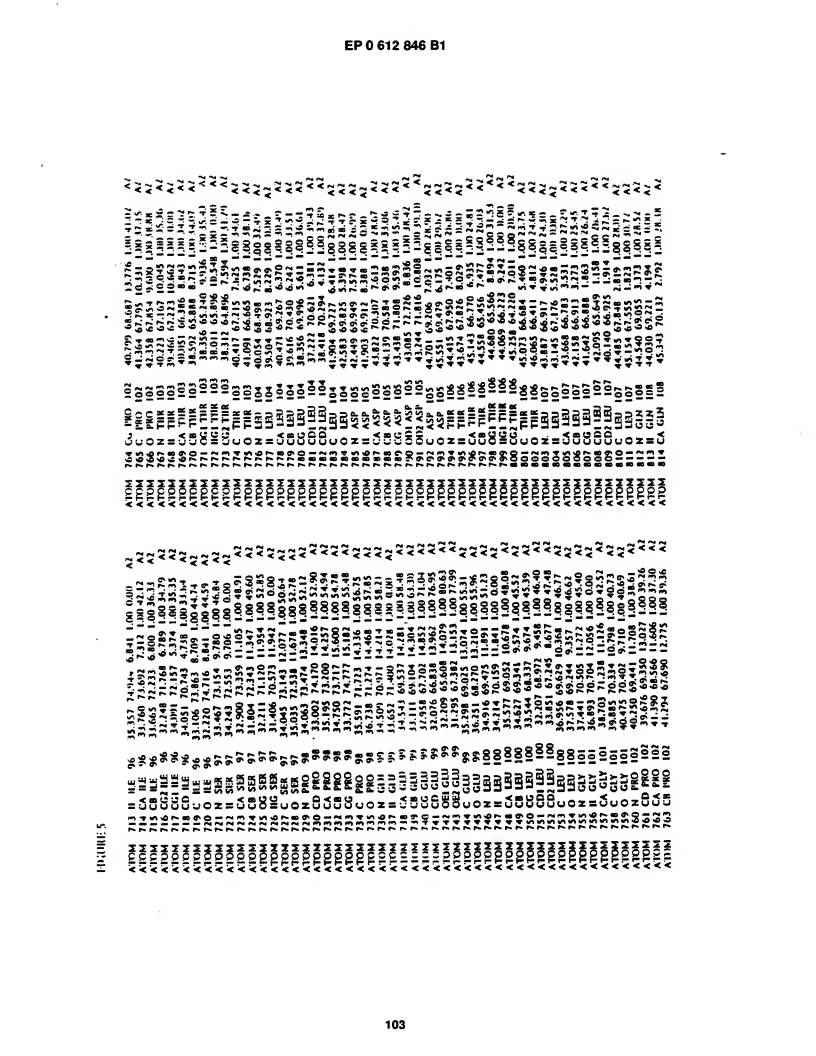

FIGURE 5

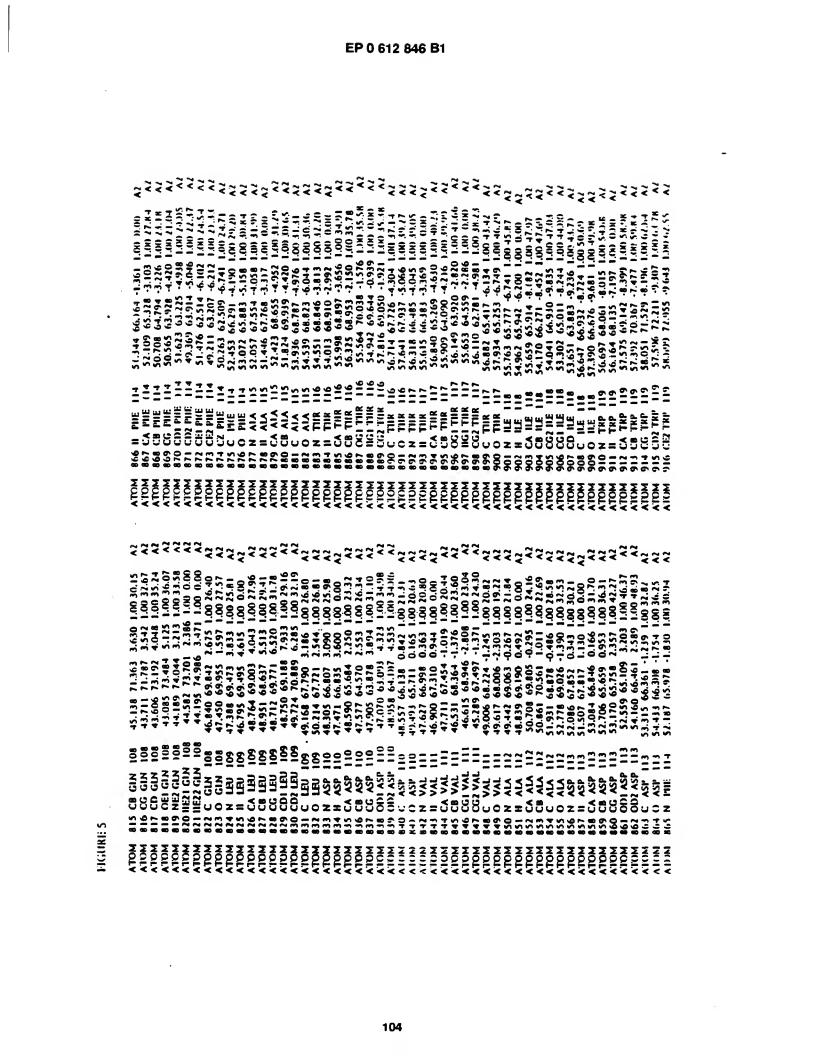

FIGURE 5

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ATOM   917 CE3 TRP  119      56.465  72.314 -10.080  1.00 66.02      A2
ATOM   918 CD1 TRP  119      59.322  71.870  -7.863  1.00 64.12      A2
ATOM   919 NE1 TRP  119      59.680  72.727  -8.784  1.00 65.00      A2
ATOM   920 HE1 TRP  119      60.568  73.140  -8.828  1.00  0.00      A2
ATOM   921 CZ2 TRP  119      58.726  73.794 -10.714  1.00 62.90      A2
ATOM   922 CZ3 TRP  119      56.469  73.157 -11.170  1.00 65.18      A2
ATOM   923 CH2 TRP  119      57.591  73.887 -11.481  1.00 64.40      A2
ATOM   924 C   TRP  119     59.021  68.664  -8.352  1.00 61.26      A2
ATOM   925 O   TRP  119     59.748  68.788  -9.343  1.00 62.12      A2
ATOM   926 N   GLN  120     59.447  68.065  -7.249  1.00 62.91      A2
ATOM   927 H   GLN  120     58.811  67.961  -6.519  1.00  0.00      A2
ATOM   928 CA  GLN  120     60.786  67.504  -7.113  1.00 65.16      A2
ATOM   929 CB  GLN  120     60.900  66.800  -5.780  1.00 66.56      A2
ATOM   930 CG  GLN  120     60.627  67.678  -4.582  1.00 67.18      A2
ATOM   931 CD  GLN  120     60.725  66.907  -3.284  1.00 67.77      A2
ATOM   932 OE1 GLN  120     61.221  67.465  -2.319  1.00 69.31      A2
ATOM   933 NE2 GLN  120     60.305  65.654  -3.129  1.00 67.39      A2
ATOM   934 HE21 GLN  120     59.903  65.174  -3.877  1.00  0.00      A2
ATOM   935 HE22 GLN  120     60.441  65.282  -2.234  1.00  0.00      A2
ATOM   936 C   GLN  120     61.169  66.509  -8.222  1.00 66.22      A2
ATOM   937 O   GLN  120     62.326  66.421  -8.662  1.00 66.50      A2
ATOM   938 N   GLN  121     60.202  65.745  -8.706  1.00 67.10      A2
ATOM   939 H   GLN  121     59.307  65.754  -8.303  1.00  0.00      A2
ATOM   940 CA  GLN  121     60.480  64.878  -9.812  1.00 68.66      A2
ATOM   941 CB  GLN  121     59.292  63.971 -10.070  1.00 67.96      A2
ATOM   942 CG  GLN  121     59.614  62.937 -11.128  1.00 68.89      A2
ATOM   943 CD  GLN  121     60.940  62.236 -10.852  1.00 71.37      A2
ATOM   944 OE1 GLN  121     61.212  61.706  -9.777  1.00 71.70      A2
ATOM   945 NE2 GLN  121     61.879  62.262 -11.786  1.00 74.41      A2
ATOM   946 HE21 GLN  121     61.707  62.729 -12.627  1.00  0.00      A2
ATOM   947 HE22 GLN  121     62.736  61.859 -11.541  1.00  0.00      A2
ATOM   948 C   GLN  121     60.760  65.743 -11.045  1.00 70.48      A2
ATOM   949 O   GLN  121     61.671  65.454 -11.822  1.00 70.94      A2
ATOM   950 N   MET  122     60.019  66.846 -11.236  1.00 71.67      A2
ATOM   951 H   MET  122     59.351  67.087 -10.555  1.00  0.00      A2
ATOM   952 CA  MET  122     60.190  67.688 -12.412  1.00 72.62      A2
ATOM   953 CB  MET  122     59.173  68.810 -12.448  1.00 73.12      A2
ATOM   954 CG  MET  122     57.880  68.343 -13.083  1.00 73.64      A2
ATOM   955 SD  MET  122     56.669  69.667 -13.295  1.00 75.44      A2
ATOM   956 CE  MET  122     55.695  69.349 -11.861  1.00 76.43      A2
ATOM   957 C   MET  122     61.566  68.281 -12.411  1.00 73.22      A2
ATOM   958 O   MET  122     62.240  68.287 -13.441  1.00 73.03      A2
ATOM   959 N   GLU  123     61.991  68.697 -11.223  1.00 74.74      A2
ATOM   960 H   GLU  123     61.377  68.617 -10.466  1.00  0.00      A2
ATOM   961 CA  GLU  123     63.305  69.262 -11.018  1.00 75.95      A2
ATOM   962 CB  GLU  123     63.484  69.665  -9.597  1.00 75.72      A2
ATOM   963 CG  GLU  123     62.644  70.906  -9.500  1.00 79.11      A2
ATOM   964 CD  GLU  123     62.651  71.529  -8.122  1.00 83.02      A2
ATOM   965 OE1 GLU  123     62.741  72.763  -8.057  1.00 84.15      A2
ATOM   966 OE2 GLU  123     62.543  70.789  -7.133  1.00 84.45      A2
ATOM   967 C   GLU  123     64.381  68.280 -11.386  1.00 77.17      A2
ATOM   968 O   GLU  123     65.092  68.558 -12.356  1.00 78.22      A2
ATOM   969 N   GLU  124     64.504  67.110 -10.765  1.00 77.66      A2
ATOM   970 H   GLU  124     63.867  66.852 -10.060  1.00  0.00      A2
ATOM   971 CA  GLU  124     65.574  66.215 -11.167  1.00 78.47      A2
ATOM   972 CB  GLU  124     65.600  65.051 -10.195  1.00 80.79      A2
ATOM   973 CG  GLU  124     64.387  64.132 -10.150  1.00 84.29      A2
ATOM   974 CD  GLU  124     64.375  63.248  -8.908  1.00 85.51      A2
ATOM   975 OE1 GLU  124     64.733  63.729  -7.824  1.00 86.84      A2
ATOM   976 OE2 GLU  124     64.006  62.075  -9.024  1.00 86.91      A2
ATOM   977 C   GLU  124     65.534  65.705 -12.612  1.00 78.01      A2
ATOM   978 O   GLU  124     66.480  65.057 -13.060  1.00 78.79      A2
ATOM   979 N   LEU  125     64.460  65.943 -13.363  1.00 77.11      A2
ATOM   980 H   LEU  125     63.666  66.340 -12.945  1.00  0.00      A2
ATOM   981 CA  LEU  125     64.387  65.583 -14.771  1.00 76.23      A2
ATOM   982 CB  LEU  125     63.061  64.832 -14.952  1.00 76.08      A2
ATOM   983 CG  LEU  125     62.392  64.382 -16.263  1.00 76.63      A2
ATOM   984 CD1 LEU  125     63.350  63.754 -17.276  1.00 76.67      A2
ATOM   985 CD2 LEU  125     61.309  63.402 -15.839  1.00 75.89      A2
ATOM   986 C   LEU  125     64.506  66.827 -15.648  1.00 75.84      A2
ATOM   987 O   LEU  125     64.360  66.788 -16.871  1.00 75.16      A2
ATOM   988 N   GLY  126     64.759  67.968 -15.027  1.00 75.90      A2
ATOM   989 H   GLY  126     64.741  67.976 -14.056  1.00  0.00      A2
ATOM   990 CA  GLY  126     64.968  69.213 -15.736  1.00 77.58      A2
ATOM   991 C   GLY  126     63.697  69.814 -16.330  1.00 78.63      A2
ATOM   992 O   GLY  126     63.735  70.736 -17.146  1.00 78.55      A2
ATOM   993 N   MET  127     62.524  69.343 -15.933  1.00 80.08      A2
ATOM   994 H   MET  127     62.522  68.603 -15.293  1.00  0.00      A2
ATOM   995 CA  MET  127     61.266  69.902 -16.415  1.00 81.46      A2
ATOM   996 CB  MET  127     60.191  68.802 -16.361  1.00 81.86      A2
ATOM   997 CG  MET  127     60.708  67.599 -17.147  1.00 82.66      A2
ATOM   998 SD  MET  127     59.682  66.115 -17.282  1.00 84.70      A2
ATOM   999 CE  MET  127     60.236  65.620 -18.900  1.00 84.83      A2
ATOM  1000 C   MET  127     60.847  71.131 -15.599  1.00 82.18      A2
ATOM  1001 OT1 MET  127     60.116  71.958 -16.142  1.00 84.86      A2
ATOM  1002 OT2 MET  127     61.267  71.285 -14.446  1.00 82.04      A2
ATOM  1003 CB  MET  138     39.323  80.595  -4.492  1.00 59.19      A3
ATOM  1004 CG  MET  138     40.123  79.298  -4.421  1.00 57.97      A3
ATOM  1005 SD  MET  138     40.561  78.973  -6.145  1.00 60.85      A3
ATOM  1006 CE  MET  138     41.129  77.310  -6.351  1.00 61.48      A3
ATOM  1007 C   MET  138     37.021  81.072  -5.454  1.00 60.26      A3
ATOM  1008 O   MET  138     36.832  82.262  -5.181  1.00 62.98      A3
ATOM  1009 HT1 MET  138     38.497  82.600  -6.075  1.00  0.00      A3
ATOM  1010 HT2 MET  138     38.313  81.757  -7.529  1.00  0.00      A3
ATOM  1011 N   MET  138     38.839  81.784  -6.639  1.00 60.49      A3
ATOM  1012 HT3 MET  138     39.865  81.816  -6.768  1.00  0.00      A3
ATOM  1013 CA  MET  138     38.445  80.672  -5.787  1.00 60.51      A3
ATOM  1014 N   PRO  139     35.995  80.242  -5.612  1.00 57.82      A4
ATOM  1015 CD  PRO  139     36.028  79.060  -6.448  1.00 58.10      A4
ATOM  1016 CA  PRO  139     34.654  80.538  -5.142  1.00 54.67      A4
ATOM  1017 CB  PRO  139     33.870  79.323  -5.525  1.00 54.54      A4
ATOM  1018 CG  PRO  139     34.945  78.290  -5.755  1.00 58.20      A4
```

FIGURE 5

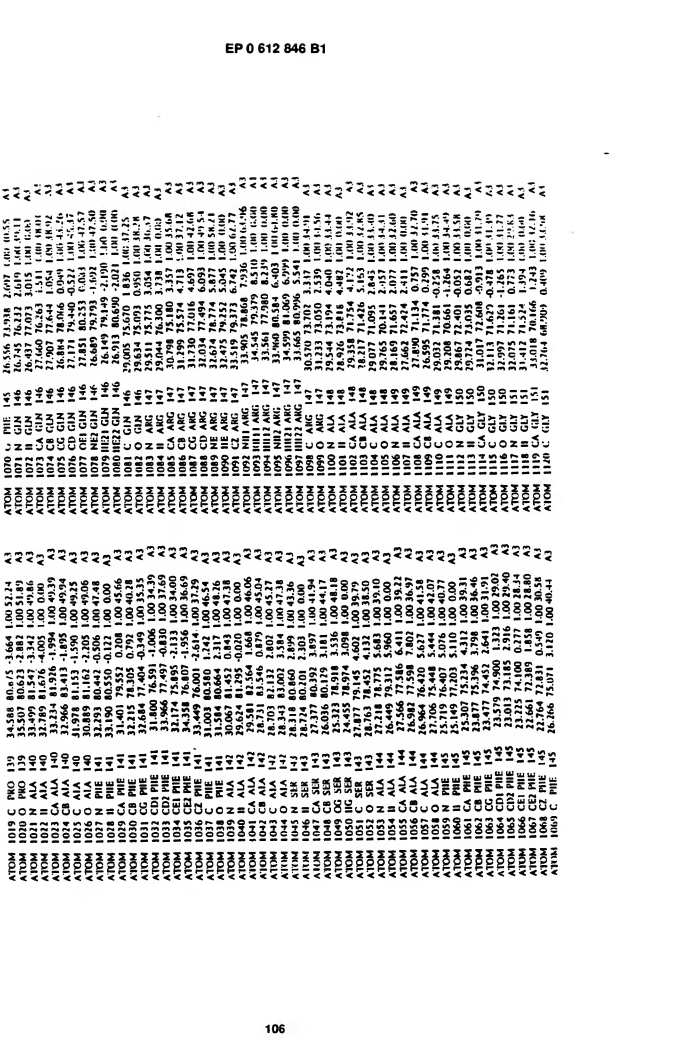

FIGURE 5

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ATOM  1121 O   GLY  151      33.664 68.501 -0.349 1.00 35.66      A3
ATOM  1122 N   VAL  152      31.486 68.418  0.451 1.00 31.87      A3
ATOM  1123 H   VAL  152      30.867 68.906  1.040 1.00  0.00      A3
ATOM  1124 CA  VAL  152      30.978 67.240 -0.275 1.00 29.61      A3
ATOM  1125 CB  VAL  152      29.419 67.145 -0.125 1.00 27.63      A3
ATOM  1126 CG1 VAL  152      28.883 66.035 -0.976 1.00 27.37      A3
ATOM  1127 CG2 VAL  152      29.002 66.786  1.279 1.00 24.74      A3
ATOM  1128 C   VAL  152      31.351 67.294 -1.762 1.00 29.91      A3
ATOM  1129 O   VAL  152      31.805 66.329 -2.393 1.00 31.75      A3
ATOM  1130 N   LEU  153      31.236 68.452 -2.361 1.00 29.26      A3
ATOM  1131 H   LEU  153      30.881 69.219 -1.860 1.00  0.00      A3
ATOM  1132 CA  LEU  153      31.559 68.607 -3.756 1.00 26.77      A3
ATOM  1133 CB  LEU  153      30.881 69.858 -4.160 1.00 28.22      A3
ATOM  1134 CG  LEU  153      29.943 69.894 -5.316 1.00 30.67      A3
ATOM  1135 CD1 LEU  153      28.580 69.281 -5.090 1.00 26.48      A3
ATOM  1136 CD2 LEU  153      29.741 71.365 -5.496 1.00 34.46      A3
ATOM  1137 C   LEU  153      33.032 68.628 -4.111 1.00 26.08      A3
ATOM  1138 O   LEU  153      33.419 68.187 -5.212 1.00 26.78      A3
ATOM  1139 N   VAL  154      33.902 69.180 -3.269 1.00 26.12      A3
ATOM  1140 H   VAL  154      33.589 69.557 -2.416 1.00  0.00      A3
ATOM  1141 CA  VAL  154      35.330 69.259 -3.611 1.00 26.23      A3
ATOM  1142 CB  VAL  154      36.057 70.299 -2.692 1.00 26.51      A3
ATOM  1143 CG1 VAL  154      37.578 70.188 -2.942 1.00 25.01      A3
ATOM  1144 CG2 VAL  154      35.528 71.728 -2.945 1.00 27.82      A3
ATOM  1145 C   VAL  154      35.933 67.850 -3.375 1.00 26.80      A3
ATOM  1146 O   VAL  154      36.678 67.363 -4.229 1.00 26.27      A3
ATOM  1147 N   ALA  155      35.635 67.241 -2.199 1.00 24.76      A3
ATOM  1148 H   ALA  155      35.084 67.758 -1.570 1.00  0.00      A3
ATOM  1149 CA  ALA  155      36.095 65.940 -1.782 1.00 25.13      A3
ATOM  1150 CB  ALA  155      35.463 65.572 -0.457 1.00 25.25      A3
ATOM  1151 C   ALA  155      35.708 64.946 -2.841 1.00 26.94      A3
ATOM  1152 O   ALA  155      36.594 64.288 -3.398 1.00 26.76      A3
ATOM  1153 N   SER  156      34.450 64.982 -3.282 1.00 26.96      A3
ATOM  1154 H   SER  156      33.790 65.577 -2.868 1.00  0.00      A3
ATOM  1155 CA  SER  156      34.034 64.105 -4.354 1.00 32.17      A3
ATOM  1156 CB  SER  156      32.531 64.319 -4.544 1.00 34.23      A3
ATOM  1157 OG  SER  156      32.000 64.195 -3.879 1.00 39.35      A3
ATOM  1158 HG  SER  156      31.120 63.815 -3.951 1.00  0.00      A3
ATOM  1159 C   SER  156      34.845 64.338 -5.632 1.00 33.46      A3
ATOM  1160 O   SER  156      35.411 63.380 -6.174 1.00 34.62      A3
ATOM  1161 N   HIS  157      35.054 65.576 -6.133 1.00 33.90      A3
ATOM  1162 H   HIS  157      34.771 66.349 -5.605 1.00  0.00      A3
ATOM  1163 CA  HIS  157      35.821 65.773 -7.383 1.00 31.19      A3
ATOM  1164 CB  HIS  157      35.707 67.209 -7.900 1.00 32.59      A3
ATOM  1165 CG  HIS  157      34.369 67.449 -8.566 1.00 31.11      A3
ATOM  1166 CD2 HIS  157      34.127 67.394 -9.928 1.00 30.78      A3
ATOM  1167 ND1 HIS  157      33.223 67.666 -7.942 1.00 32.36      A3
ATOM  1168 HD1 HIS  157      33.080 67.773 -6.979 1.00  0.00      A3
ATOM  1169 CE1 HIS  157      32.293 67.732 -8.875 1.00 32.01      A3
ATOM  1170 NE2 HIS  157      32.838 67.571 -10.060 1.00 29.18     A3
ATOM  1171 HE2 HIS  157      32.327 67.621 -10.895 1.00  0.00     A3

ATOM  1172 C   HIS  157      37.291 65.476 -7.269 1.00 29.68      A3
ATOM  1173 O   HIS  157      37.950 65.059 -8.219 1.00 29.65      A3
ATOM  1174 N   LEU  158      37.801 65.669 -6.071 1.00 29.24      A3
ATOM  1175 H   LEU  158      37.213 65.901 -5.326 1.00  0.00      A3
ATOM  1176 CA  LEU  158      39.216 65.479 -5.826 1.00 31.94      A3
ATOM  1177 CB  LEU  158      39.609 65.949 -4.373 1.00 28.66      A3
ATOM  1178 CG  LEU  158      41.008 65.751 -3.859 1.00 34.32      A3
ATOM  1179 CD1 LEU  158      41.990 66.378 -4.776 1.00 24.87      A3
ATOM  1180 CD2 LEU  158      41.099 66.330 -2.477 1.00 24.86      A3
ATOM  1181 C   LEU  158      29.468 63.994 -6.027 1.00 31.40      A3
ATOM  1182 O   LEU  158      40.298 63.609 -6.844 1.00 30.58      A3
ATOM  1183 N   GLN  159      38.653 63.215 -5.340 1.00 33.54      A3
ATOM  1184 H   GLN  159      38.011 63.676 -4.748 1.00  0.00      A3
ATOM  1185 CA  GLN  159      38.594 61.792 -5.442 1.00 35.73      A3
ATOM  1186 CB  GLN  159      37.308 61.492 -4.813 1.00 37.26      A3
ATOM  1187 CG  GLN  159      37.064 60.063 -4.520 1.00 45.01      A3
ATOM  1188 CD  GLN  159      37.755 59.611 -3.256 1.00 46.24      A3
ATOM  1189 OE1 GLN  159      38.142 58.443 -3.232 1.00 48.29      A3
ATOM  1190 NE2 GLN  159      37.936 60.456 -2.224 1.00 47.82      A3
ATOM  1191 HE21 GLN  159      37.575 61.364 -2.289 1.00  0.00      A3
ATOM  1192 HE22 GLN  159      38.412 60.101 -1.447 1.00  0.00      A3
ATOM  1193 C   GLN  159      38.686 61.381 -6.921 1.00 36.24      A3
ATOM  1194 O   GLN  159      39.632 60.690 -7.324 1.00 38.97      A3
ATOM  1195 N   SER  160      37.824 61.896 -7.796 1.00 35.58      A3
ATOM  1196 H   SER  160      37.142 62.540 -7.498 1.00  0.00      A3
ATOM  1197 CA  SER  160      37.869 61.564 -9.203 1.00 34.96      A3
ATOM  1198 CB  SER  160      36.645 62.100 -9.863 1.00 37.54      A3
ATOM  1199 OG  SER  160      35.587 62.434 -8.942 1.00 44.81      A3
ATOM  1200 HG  SER  160      35.340 61.689 -8.387 1.00  0.00      A3
ATOM  1201 C   SER  160      39.090 62.095 -9.922 1.00 34.65      A3
ATOM  1202 O   SER  160      39.605 61.382 -10.785 1.00 35.42      A3
ATOM  1203 N   PHE  161      39.615 63.293 -9.595 1.00 33.82      A3
ATOM  1204 H   PHE  161      39.203 63.796 -8.864 1.00  0.00      A3
ATOM  1205 CA  PHE  161      40.820 63.850 -10.218 1.00 31.21     A3
ATOM  1206 CB  PHE  161      41.110 65.254 -9.629 1.00 28.28      A3
ATOM  1207 CG  PHE  161      42.455 65.881 -10.062 1.00 24.92     A3
ATOM  1208 CD1 PHE  161      42.696 66.228 -11.389 1.00 22.58     A3
ATOM  1209 CD2 PHE  161      43.464 66.021 -9.135 1.00 23.63      A3
ATOM  1210 CE1 PHE  161      43.941 66.695 -11.767 1.00 21.06     A3
ATOM  1211 CE2 PHE  161      44.701 66.495 -9.528 1.00 20.28      A3
ATOM  1212 CZ  PHE  161      44.939 66.826 -10.832 1.00 17.01     A3
ATOM  1213 C   PHE  161      42.008 62.907 -9.943 1.00 31.77      A3
ATOM  1214 O   PHE  161      42.786 62.578 -10.845 1.00 32.63     A3
ATOM  1215 N   LEU  162      42.117 62.434 -8.690 1.00 31.67      A3
ATOM  1216 H   LEU  162      41.420 62.691 -8.054 1.00  0.00      A3
ATOM  1217 CA  LEU  162      43.186 61.574 -8.232 1.00 31.29      A3
ATOM  1218 CB  LEU  162      43.204 61.433 -6.743 1.00 25.84      A3
ATOM  1219 CG  LEU  162      43.693 62.674 -6.003 1.00 26.02      A3
ATOM  1220 CD1 LEU  162      43.594 62.455 -4.516 1.00 15.24      A3
ATOM  1221 CD2 LEU  162      45.107 62.994 -6.415 1.00 27.04      A3
ATOM  1222 C   LEU  162      43.061 60.212 -8.813 1.00 34.24      A3
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FIGURE 5

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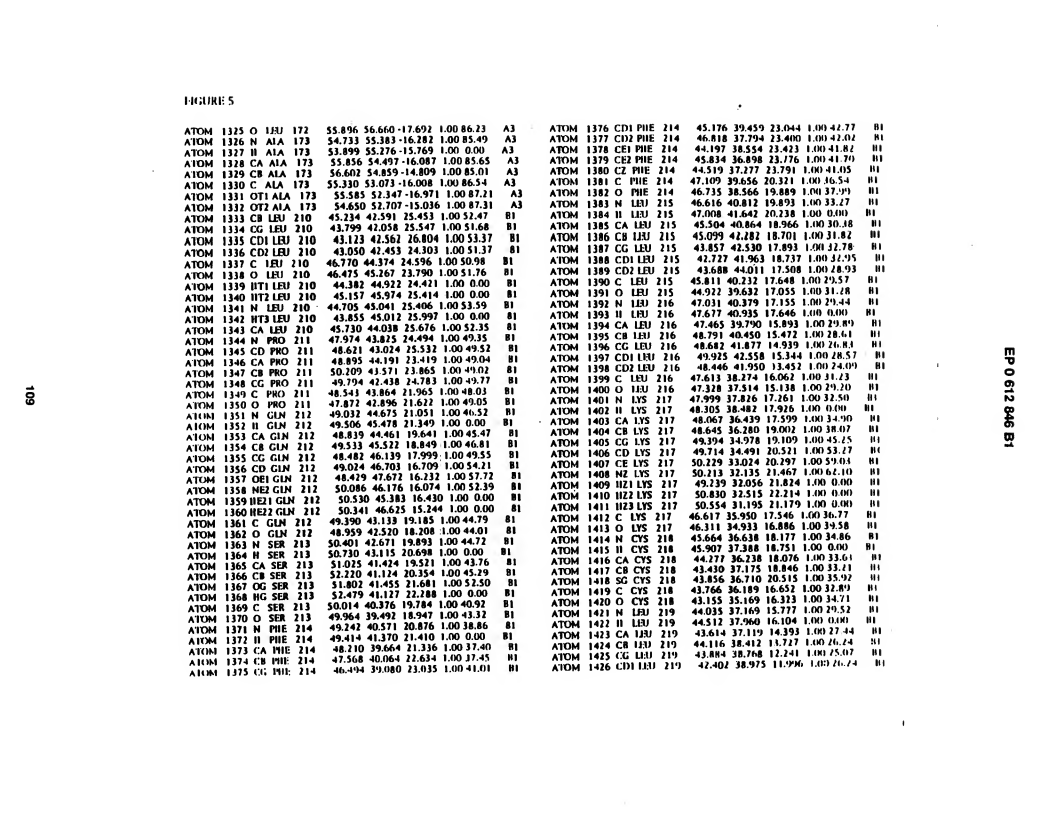
ATOM  1223 O   LEU  162     44.107  59.654  -9.070  1.00 36.51      A3
ATOM  1224 N   GLU  163     41.926  59.589  -9.082  1.00 37.24      A3
ATOM  1225 H   GLU  163     41.072  60.002  -8.826  1.00  0.00      A3
ATOM  1226 CA  GLU  163     41.975  58.327  -9.771  1.00 40.47      A3
ATOM  1227 CB  GLU  163     40.566  57.716  -9.835  1.00 45.38      A3
ATOM  1228 CG  GLU  163     40.264  56.975  -8.526  1.00 51.84      A3
ATOM  1229 CD  GLU  163     41.291  55.889  -8.126  1.00 57.97      A3
ATOM  1230 OE1 GLU  163     40.897  54.722  -8.092  1.00 62.01      A3
ATOM  1231 OE2 GLU  163     42.466  56.180  -7.832  1.00 59.17      A3
ATOM  1232 C   GLU  163     42.586  58.430 -11.142  1.00 41.34      A3
ATOM  1233 O   GLU  163     43.456  57.633 -11.486  1.00 42.17      A3
ATOM  1234 N   VAL  164     42.257  59.436 -11.920  1.00 42.28      A3
ATOM  1235 H   VAL  164     41.589  60.091 -11.615  1.00  0.00      A3
ATOM  1236 CA  VAL  164     42.911  59.609 -13.187  1.00 44.13      A3
ATOM  1237 CB  VAL  164     42.207  60.711 -13.940  1.00 45.52      A3
ATOM  1238 CG1 VAL  164     42.892  60.975 -15.278  1.00 48.79      A3
ATOM  1239 CG2 VAL  164     40.786  60.269 -14.226  1.00 46.09      A3
ATOM  1240 C   VAL  164     44.386  59.933 -12.991  1.00 46.13      A3
ATOM  1241 O   VAL  164     45.192  59.473 -13.794  1.00 45.99      A3
ATOM  1242 N   SER  165     44.879  60.677 -12.006  1.00 49.51      A3
ATOM  1243 H   SER  165     44.287  61.173 -11.396  1.00  0.00      A3
ATOM  1244 CA  SER  165     46.325  60.845 -11.895  1.00 53.44      A3
ATOM  1245 CB  SER  165     46.715  61.796 -10.775  1.00 54.77      A3
ATOM  1246 OG  SER  165     46.049  61.618  -9.530  1.00 59.99      A3
ATOM  1247 HG  SER  165     45.997  60.694  -9.261  1.00  0.00      A3
ATOM  1248 C   SER  165     46.958  59.502 -12.050  1.00 55.15      A3
ATOM  1249 O   SER  165     48.028  59.227 -12.148  1.00 55.02      A3
ATOM  1250 N   TYR  166     46.239  58.645 -10.900  1.00 58.57      A3
ATOM  1251 H   TYR  166     45.374  58.948 -10.549  1.00  0.00      A3
ATOM  1252 CA  TYR  166     46.617  57.273 -10.625  1.00 61.42      A3
ATOM  1253 CB  TYR  166     45.543  56.653  -9.680  1.00 64.05      A3
ATOM  1254 CG  TYR  166     45.502  55.138  -9.682  1.00 69.00      A3
ATOM  1255 CD1 TYR  166     44.389  54.501 -10.185  1.00 71.64      A3
ATOM  1256 CE1 TYR  166     44.367  53.130 -10.191  1.00 73.45      A3
ATOM  1257 CD2 TYR  166     46.594  54.409  -9.257  1.00 71.27      A3
ATOM  1258 CE2 TYR  166     46.584  53.040  -9.346  1.00 72.92      A3
ATOM  1259 CZ  TYR  166     45.468  52.417  -9.862  1.00 75.71      A3
ATOM  1260 OH  TYR  166     45.474  51.038 -10.016  1.00 80.61      A3
ATOM  1261 HH  TYR  166     44.571  50.736 -10.134  1.00  0.00      A3
ATOM  1262 C   TYR  166     46.712  56.567 -11.987  1.00 62.34      A3
ATOM  1263 O   TYR  166     47.766  55.981 -12.282  1.00 63.25      A3
ATOM  1264 N   ALA  167     45.727  56.622 -12.884  1.00 61.27      A3
ATOM  1265 H   ALA  167     44.893  57.089 -12.678  1.00  0.00      A3
ATOM  1266 CA  ALA  167     45.933  55.982 -14.159  1.00 61.47      A3
ATOM  1267 CB  ALA  167     44.608  55.904 -14.904  1.00 60.98      A3
ATOM  1268 C   ALA  167     46.982  56.694 -15.020  1.00 62.19      A3
ATOM  1269 O   ALA  167     47.719  56.000 -15.734  1.00 62.63      A3
ATOM  1270 N   VAL  168     47.210  58.011 -14.991  1.00 63.37      A3
ATOM  1271 H   VAL  168     46.756  58.570 -14.330  1.00  0.00      A3
ATOM  1272 CA  VAL  168     48.174  58.593 -15.923  1.00 65.62      A3
ATOM  1273 CB  VAL  168     48.061  60.121 -16.131  1.00 66.30      A3
ATOM  1274 CG1 VAL  168     46.687  60.431 -16.706  1.00 66.78      A3
ATOM  1275 CG2 VAL  168     48.278  60.879 -14.840  1.00 68.47      A3
ATOM  1276 C   VAL  168     49.579  58.339 -15.469  1.00 66.45      A3
ATOM  1277 O   VAL  168     50.458  58.183 -16.312  1.00 66.22      A3
ATOM  1278 N   LEU  169     49.823  58.241 -14.177  1.00 68.83      A3
ATOM  1279 H   LEU  169     49.102  58.404 -13.536  1.00  0.00      A3
ATOM  1280 CA  LEU  169     51.141  57.899 -13.695  1.00 71.81      A3
ATOM  1281 CB  LEU  169     51.249  58.228 -12.188  1.00 71.51      A3
ATOM  1282 CG  LEU  169     51.137  59.732 -11.813  1.00 70.68      A3
ATOM  1283 CD1 LEU  169     51.187  59.826 -10.298  1.00 69.49      A3
ATOM  1284 CD2 LEU  169     52.223  60.580 -12.491  1.00 68.49      A3
ATOM  1285 C   LEU  169     51.333  56.414 -13.979  1.00 73.61      A3
ATOM  1286 O   LEU  169     52.408  56.013 -14.429  1.00 74.75      A3
ATOM  1287 N   ARG  170     50.309  55.583 -13.819  1.00 75.45      A3
ATOM  1288 H   ARG  170     49.488  55.923 -13.399  1.00  0.00      A3
ATOM  1289 CA  ARG  170     50.364  54.179 -14.199  1.00 78.17      A3
ATOM  1290 CB  ARG  170     48.944  53.642 -14.004  1.00 78.45      A3
ATOM  1291 CG  ARG  170     48.394  52.506 -14.871  1.00 78.17      A3
ATOM  1292 CD  ARG  170     48.744  51.181 -14.271  1.00 77.25      A3
ATOM  1293 NE  ARG  170     48.123  51.120 -12.970  1.00 76.15      A3
ATOM  1294 HE  ARG  170     47.245  51.528 -12.824  1.00 76.00      A3
ATOM  1295 CZ  ARG  170     48.758  50.547 -11.970  1.00 76.14      A3
ATOM  1296 NH1 ARG  170     49.973  50.017 -12.112  1.00 76.84      A3
ATOM  1297 HH11 ARG  170     50.441  50.030 -12.994  1.00  0.00      A3
ATOM  1298 HH12 ARG  170     50.406  49.570 -11.329  1.00  0.00      A3
ATOM  1299 NH2 ARG  170     48.147  50.492 -10.806  1.00 77.02      A3
ATOM  1300 HH21 ARG  170     47.237  50.890 -10.714  1.00  0.00      A3
ATOM  1301 HH22 ARG  170     48.586  50.052 -10.023  1.00  0.00      A3
ATOM  1302 C   ARG  170     50.870  54.052 -15.647  1.00 79.84      A3
ATOM  1303 O   ARG  170     51.924  53.470 -15.908  1.00 80.07      A3
ATOM  1304 N   HIS  171     50.193  54.663 -16.611  1.00 81.38      A3
ATOM  1305 H   HIS  171     49.433  55.234 -16.359  1.00  0.00      A3
ATOM  1306 CA  HIS  171     50.663  54.597 -17.970  1.00 84.03      A3
ATOM  1307 CB  HIS  171     49.598  55.054 -18.902  1.00 86.82      A3
ATOM  1308 CG  HIS  171     48.496  54.037 -19.147  1.00 90.73      A3
ATOM  1309 CD2 HIS  171     47.467  53.765 -18.272  1.00 91.35      A3
ATOM  1310 ND1 HIS  171     48.308  53.301 -20.248  1.00 92.24      A3
ATOM  1311 HD1 HIS  171     48.887  53.287 -21.044  1.00  0.00      A3
ATOM  1312 CE1 HIS  171     47.204  52.605 -20.077  1.00 92.41      A3
ATOM  1313 NE2 HIS  171     46.711  52.892 -18.891  1.00 92.59      A3
ATOM  1314 HE2 HIS  171     45.884  52.511 -18.518  1.00  0.00      A3
ATOM  1315 C   HIS  171     51.907  55.446 -18.232  1.00 85.42      A3
ATOM  1316 O   HIS  171     52.440  55.352 -19.344  1.00 85.98      A3
ATOM  1317 N   LEU  172     52.359  56.307 -17.302  1.00 86.13      A3
ATOM  1318 H   LEU  172     51.870  56.411 -16.463  1.00  0.00      A3
ATOM  1319 CA  LEU  172     53.550  57.133 -17.496  1.00 86.02      A3
ATOM  1320 CB  LEU  172     53.500  58.357 -16.607  1.00 86.41      A3
ATOM  1321 CG  LEU  172     54.022  59.658 -17.203  1.00 87.48      A3
ATOM  1322 CD1 LEU  172     53.436  59.939 -18.596  1.00 87.68      A3
ATOM  1323 CD2 LEU  172     53.645  60.778 -16.251  1.00 87.95      A3
ATOM  1324 C   LEU  172     54.813  56.357 -17.180  1.00 85.92      A3
```

FIGURE 5



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ATOM  1325  O   LEU  172      55.896  56.660 -17.692  1.00 86.23      A3
ATOM  1326  N   ALA  173      54.733  55.383 -16.282  1.00 85.49      A3
ATOM  1327  H   ALA  173      53.899  55.276 -15.769  1.00  0.00      A3
ATOM  1328  CA  ALA  173      55.856  54.497 -16.087  1.00 85.65      A3
ATOM  1329  CB  ALA  173      56.602  54.859 -14.809  1.00 85.01      A3
ATOM  1330  C   ALA  173      55.330  53.073 -16.008  1.00 86.54      A3
ATOM  1331  OT1 ALA  173      55.585  52.347 -16.971  1.00 87.21      A3
ATOM  1332  OT2 ALA  173      54.650  52.707 -15.036  1.00 87.31      A3
ATOM  1333  CB  LEU  210      45.234  42.591  25.453  1.00 52.47      B1
ATOM  1334  CG  LEU  210      43.799  42.058  25.547  1.00 51.68      B1
ATOM  1335  CD1 LEU  210      43.123  42.562  26.804  1.00 53.37      B1
ATOM  1336  CD2 LEU  210      43.050  42.453  24.303  1.00 51.37      B1
ATOM  1337  C   LEU  210      46.770  44.374  24.596  1.00 50.98      B1
ATOM  1338  O   LEU  210      46.475  45.267  23.790  1.00 51.76      B1
ATOM  1339  HT1 LEU  210      44.382  44.922  24.421  1.00  0.00      B1
ATOM  1340  HT2 LEU  210      45.157  45.974  25.414  1.00  0.00      B1
ATOM  1341  N   LEU  210      44.705  45.041  25.406  1.00 53.59      B1
ATOM  1342  HT3 LEU  210      43.855  45.012  25.997  1.00  0.00      B1
ATOM  1343  CA  LEU  210      45.730  44.038  25.676  1.00 52.35      B1
ATOM  1344  N   PRO  211      47.974  43.825  24.494  1.00 49.35      B1
ATOM  1345  CD  PRO  211      48.621  43.024  25.532  1.00 49.52      B1
ATOM  1346  CA  PRO  211      48.895  44.191  23.419  1.00 49.04      B1
ATOM  1347  CB  PRO  211      50.209  43.571  23.865  1.00 49.02      B1
ATOM  1348  CG  PRO  211      49.794  42.438  24.783  1.00 49.77      B1
ATOM  1349  C   PRO  211      48.543  43.864  21.965  1.00 48.28      B1
ATOM  1350  O   PRO  211      47.872  42.896  21.622  1.00 49.05      B1
ATOM  1351  N   GLN  212      49.032  44.675  21.051  1.00 46.52      B1
ATOM  1352  H   GLN  212      49.506  45.478  21.349  1.00  0.00      B1
ATOM  1353  CA  GLN  212      48.839  44.461  19.641  1.00 45.47      B1
ATOM  1354  CB  GLN  212      49.533  45.525  18.845  1.00 46.81      B1
ATOM  1355  CG  GLN  212      48.482  46.139  17.999  1.00 49.55      B1
ATOM  1356  CD  GLN  212      49.024  46.703  16.709  1.00 54.21      B1
ATOM  1357  OE1 GLN  212      48.429  47.672  16.232  1.00 57.72      B1
ATOM  1358  NE2 GLN  212      50.086  46.176  16.074  1.00 52.59      B1
ATOM  1359  HE21 GLN  212      50.530  45.383  16.430  1.00  0.00      B1
ATOM  1360  HE22 GLN  212      50.341  46.625  15.244  1.00  0.00      B1
ATOM  1361  C   GLN  212      49.390  43.133  19.185  1.00 44.79      B1
ATOM  1362  O   GLN  212      48.959  42.520  18.208  1.00 44.01      B1
ATOM  1363  N   SER  213      50.401  42.671  19.893  1.00 44.72      B1
ATOM  1364  H   SER  213      50.730  43.115  20.698  1.00  0.00      B1
ATOM  1365  CA  SER  213      51.025  41.424  19.521  1.00 43.76      B1
ATOM  1366  CB  SER  213      52.220  41.124  20.354  1.00 45.29      B1
ATOM  1367  OG  SER  213      51.802  41.455  21.681  1.00 52.50      B1
ATOM  1368  HG  SER  213      52.479  41.127  22.288  1.00  0.00      B1
ATOM  1369  C   SER  213      50.014  40.376  19.784  1.00 40.92      B1
ATOM  1370  O   SER  213      49.964  39.492  18.947  1.00 43.32      B1
ATOM  1371  N   PHE  214      49.242  40.571  20.876  1.00 38.86      B1
ATOM  1372  H   PHE  214      49.414  41.370  21.410  1.00  0.00      B1
ATOM  1373  CA  PHE  214      48.210  39.664  21.336  1.00 37.40      B1
ATOM  1374  CB  PHE  214      47.568  40.064  22.634  1.00 37.45      B1
ATOM  1375  CG  PHE  214      46.494  39.080  23.035  1.00 41.01      B1
ATOM  1376  CD1 PHE  214      45.176  39.459  23.044  1.00 41.77      B1
ATOM  1377  CD2 PHE  214      46.818  37.794  23.400  1.00 42.02      B1
ATOM  1378  CE1 PHE  214      44.197  38.554  23.423  1.00 41.82      B1
ATOM  1379  CE2 PHE  214      45.834  36.898  23.776  1.00 41.70      B1
ATOM  1380  CZ  PHE  214      44.519  37.277  23.791  1.00 41.05      B1
ATOM  1381  C   PHE  214      47.109  39.656  20.321  1.00 36.54      B1
ATOM  1382  O   PHE  214      46.735  38.566  19.889  1.00 37.99      B1
ATOM  1383  N   LEU  215      46.616  40.812  19.893  1.00 33.27      B1
ATOM  1384  H   LEU  215      47.008  41.642  20.238  1.00  0.00      B1
ATOM  1385  CA  LEU  215      45.504  40.864  18.966  1.00 30.38      B1
ATOM  1386  CB  LEU  215      45.099  42.282  18.701  1.00 31.82      B1
ATOM  1387  CG  LEU  215      43.857  42.530  17.893  1.00 32.78      B1
ATOM  1388  CD1 LEU  215      42.727  41.963  18.737  1.00 32.95      B1
ATOM  1389  CD2 LEU  215      43.688  44.011  17.508  1.00 28.93      B1
ATOM  1390  C   LEU  215      45.811  40.232  17.648  1.00 29.57      B1
ATOM  1391  O   LEU  215      44.922  39.632  17.055  1.00 31.28      B1
ATOM  1392  N   LEU  216      47.031  40.379  17.155  1.00 29.44      B1
ATOM  1393  H   LEU  216      47.677  40.935  17.646  1.00  0.00      B1
ATOM  1394  CA  LEU  216      47.465  39.790  15.893  1.00 29.89      B1
ATOM  1395  CB  LEU  216      48.791  40.450  15.472  1.00 28.61      B1
ATOM  1396  CG  LEU  216      48.682  41.877  14.939  1.00 26.83      B1
ATOM  1397  CD1 LEU  216      49.925  42.558  15.344  1.00 28.57      B1
ATOM  1398  CD2 LEU  216      48.446  41.950  13.452  1.00 24.09      B1
ATOM  1399  C   LEU  216      47.613  38.274  16.062  1.00 31.23      B1
ATOM  1400  O   LEU  216      47.328  37.514  15.138  1.00 29.20      B1
ATOM  1401  N   LYS  217      47.999  37.826  17.261  1.00 32.50      B1
ATOM  1402  H   LYS  217      48.305  38.482  17.926  1.00  0.00      B1
ATOM  1403  CA  LYS  217      48.066  36.439  17.595  1.00 34.90      B1
ATOM  1404  CB  LYS  217      48.645  36.280  19.002  1.00 38.07      B1
ATOM  1405  CG  LYS  217      49.394  34.978  19.109  1.00 45.25      B1
ATOM  1406  CD  LYS  217      49.714  34.491  20.521  1.00 53.27      B1
ATOM  1407  CE  LYS  217      50.229  33.024  20.297  1.00 59.04      B1
ATOM  1408  NZ  LYS  217      50.213  32.135  21.467  1.00 62.10      B1
ATOM  1409  HZ1 LYS  217      49.239  32.056  21.824  1.00  0.00      B1
ATOM  1410  HZ2 LYS  217      50.830  32.515  22.214  1.00  0.00      B1
ATOM  1411  HZ3 LYS  217      50.554  31.195  21.179  1.00  0.00      B1
ATOM  1412  C   LYS  217      46.617  35.950  17.546  1.00 36.77      B1
ATOM  1413  O   LYS  217      46.311  34.933  16.886  1.00 39.58      B1
ATOM  1414  N   CYS  218      45.664  36.638  18.177  1.00 34.86      B1
ATOM  1415  H   CYS  218      45.907  37.388  18.751  1.00  0.00      B1
ATOM  1416  CA  CYS  218      44.277  36.238  18.076  1.00 33.61      B1
ATOM  1417  CB  CYS  218      43.430  37.175  18.846  1.00 33.21      B1
ATOM  1418  SG  CYS  218      43.856  36.710  20.515  1.00 35.92      B1
ATOM  1419  C   CYS  218      43.766  36.189  16.652  1.00 32.89      B1
ATOM  1420  O   CYS  218      43.155  35.169  16.323  1.00 34.71      B1
ATOM  1421  N   LEU  219      44.035  37.169  15.777  1.00 29.52      B1
ATOM  1422  H   LEU  219      44.512  37.960  16.104  1.00  0.00      B1
ATOM  1423  CA  LEU  219      43.614  37.119  14.393  1.00 27.44      B1
ATOM  1424  CB  LEU  219      44.116  38.412  13.727  1.00 26.24      B1
ATOM  1425  CG  LEU  219      43.884  38.768  12.241  1.00 25.07      B1
ATOM  1426  CD1 LEU  219      42.402  38.975  11.996  1.00 26.24      B1
```

FIGURE 5

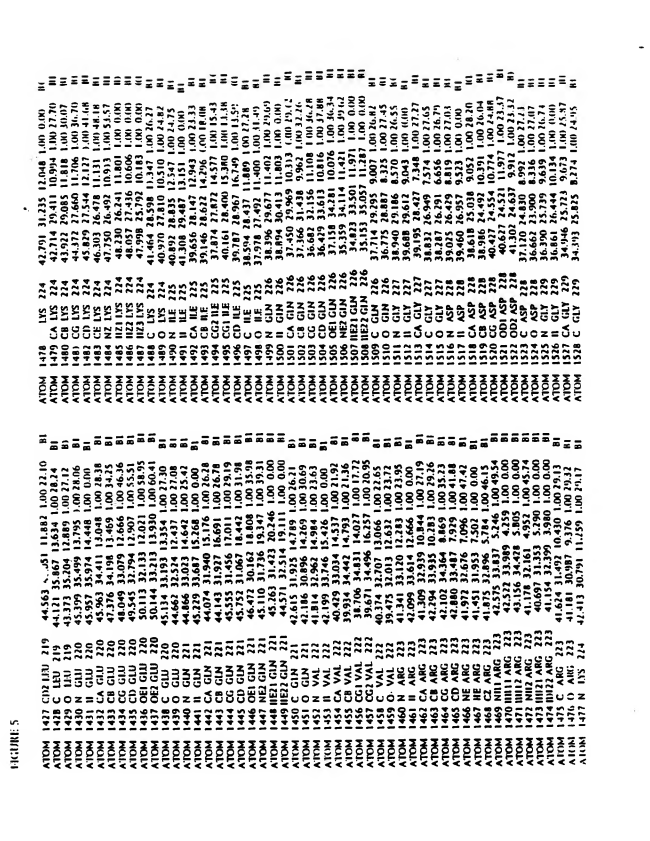

FIGURE 5

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ATOM  1529 O   GLY  229      33.370 25.222  7.956 1.00 25.73      B1
ATOM  1530 N   ALA  230      35.058 26.541  7.391 1.00 23.97      B1
ATOM  1531 H   ALA  230      35.871 27.026  7.654 1.00 0.00       B1
ATOM  1532 CA  ALA  230      34.530 26.688  6.061 1.00 25.94      B1
ATOM  1533 CB  ALA  230      35.193 27.852  5.312 1.00 19.76      B1
ATOM  1534 C   ALA  230      34.794 25.403  5.304 1.00 29.42      B1
ATOM  1535 O   ALA  230      34.014 25.061  4.423 1.00 32.07      B1
ATOM  1536 N   ALA  231      35.878 24.671  5.572 1.00 32.16      B1
ATOM  1537 H   ALA  231      36.556 25.045  6.175 1.00 0.00       B1
ATOM  1538 CA  ALA  231      36.141 23.364  4.957 1.00 31.99      B1
ATOM  1539 CB  ALA  231      37.489 22.847  5.428 1.00 31.77      B1
ATOM  1540 C   ALA  231      35.060 22.361  5.386 1.00 32.99      B1
ATOM  1541 O   ALA  231      34.599 21.575  4.576 1.00 34.12      B1
ATOM  1542 N   LEU  232      34.662 22.309  6.652 1.00 33.30      B1
ATOM  1543 H   LEU  232      35.174 22.861  7.284 1.00 0.00       B1
ATOM  1544 CA  LEU  232      33.558 21.506  7.165 1.00 35.33      B1
ATOM  1545 CB  LEU  232      33.279 21.783  8.626 1.00 34.22      B1
ATOM  1546 CG  LEU  232      32.410 20.861  9.394 1.00 33.16      B1
ATOM  1547 CD1 LEU  232      33.191 19.545  9.453 1.00 34.59      B1
ATOM  1548 CD2 LEU  232      32.107 21.381 10.800 1.00 31.32      B1
ATOM  1549 C   LEU  232      32.271 21.829  6.440 1.00 36.65      B1
ATOM  1550 O   LEU  232      31.703 20.986  5.749 1.00 36.42      B1
ATOM  1551 N   GLN  233      31.836 23.084  6.570 1.00 38.89      B1
ATOM  1552 H   GLN  233      32.378 23.719  7.087 1.00 0.00       B1
ATOM  1553 CA  GLN  233      30.637 23.579  5.933 1.00 40.02      B1
ATOM  1554 CB  GLN  233      30.572 25.072  6.162 1.00 42.25      B1
ATOM  1555 CG  GLN  233      30.290 25.398  7.626 1.00 48.22      B1
ATOM  1556 CD  GLN  233      30.021 26.879  7.983 1.00 53.75      B1
ATOM  1557 OE1 GLN  233      30.799 27.810  7.718 1.00 55.93      B1
ATOM  1558 NE2 GLN  233      28.909 27.215  8.634 1.00 56.51      B1
ATOM  1559 HE21 GLN  233      28.810 28.144  8.902 1.00 0.00       B1
ATOM  1560 HE22 GLN  233      28.205 26.533  8.710 1.00 0.00       B1
ATOM  1561 C   GLN  233      30.635 23.243  4.447 1.00 39.70      B1
ATOM  1562 O   GLN  233      29.631 22.777  3.898 1.00 40.20      B1
ATOM  1563 N   GLU  234      31.744 23.377  3.736 1.00 39.32      B1
ATOM  1564 H   GLU  234      32.544 23.750  4.163 1.00 0.00       B1
ATOM  1565 CA  GLU  234      31.809 23.025  2.329 1.00 39.23      B1
ATOM  1566 CB  GLU  234      33.155 23.434  1.811 1.00 40.25      B1
ATOM  1567 CG  GLU  234      33.292 23.028  0.383 1.00 47.69      B1
ATOM  1568 CD  GLU  234      34.733 23.056 -0.073 1.00 53.40      B1
ATOM  1569 OE1 GLU  234      34.986 23.721 -1.100 1.00 53.78      B1
ATOM  1570 OE2 GLU  234      35.568 22.400  0.590 1.00 57.55      B1
ATOM  1571 C   GLU  234      31.580 21.535  2.136 1.00 37.09      B1
ATOM  1572 O   GLU  234      30.884 21.217  1.188 1.00 36.67      B1
ATOM  1573 N   LYS  235      32.092 20.623  2.986 1.00 37.27      B1
ATOM  1574 H   LYS  235      32.668 20.965  3.706 1.00 0.00       B1
ATOM  1575 CA  LYS  235      31.832 19.177  2.942 1.00 36.27      B1
ATOM  1576 CB  LYS  235      32.516 18.365  3.997 1.00 34.92      B1
ATOM  1577 CG  LYS  235      33.978 18.483  4.107 1.00 38.47      B1
ATOM  1578 CD  LYS  235      34.762 17.999  2.921 1.00 38.07      B1
ATOM  1579 CE  LYS  235      36.192 18.051  3.460 1.00 39.15      B1
ATOM  1580 NZ  LYS  235      37.117 17.460  2.521 1.00 41.34      B1
ATOM  1581 HZ1 LYS  235      37.080 17.978  1.622 1.00 0.00       B1
ATOM  1582 HZ2 LYS  235      36.854 16.466  2.363 1.00 0.00       B1
ATOM  1583 HZ3 LYS  235      38.080 17.497  2.911 1.00 0.00       B1
ATOM  1584 C   LYS  235      30.363 18.847  3.204 1.00 35.20      B1
ATOM  1585 O   LYS  235      29.722 18.192  2.363 1.00 35.60      B1
ATOM  1586 N   LEU  236      29.807 19.332  4.301 1.00 33.53      B1
ATOM  1587 H   LEU  236      30.363 19.888  4.885 1.00 0.00       B1
ATOM  1588 CA  LEU  236      28.417 19.116  4.641 1.00 32.30      B1
ATOM  1589 CB  LEU  236      28.093 19.918  5.894 1.00 28.65      B1
ATOM  1590 CG  LEU  236      28.791 19.441  7.148 1.00 28.24      B1
ATOM  1591 CD1 LEU  236      28.703 20.460  8.268 1.00 24.14      B1
ATOM  1592 CD2 LEU  236      28.132 18.163  7.587 1.00 26.66      B1
ATOM  1593 C   LEU  236      27.590 19.574  3.453 1.00 34.69      B1
ATOM  1594 O   LEU  236      26.691 18.849  3.064 1.00 35.13      B1
ATOM  1595 N   CYS  237      27.870 20.670  2.753 1.00 34.49      B1
ATOM  1596 H   CYS  237      28.611 21.251  3.025 1.00 0.00       B1
ATOM  1597 CA  CYS  237      27.064 21.016  1.606 1.00 34.95      B1
ATOM  1598 C   CYS  237      27.324 20.090  0.451 1.00 35.97      B1
ATOM  1599 O   CYS  237      26.360 19.573 -0.089 1.00 36.09      B1
ATOM  1600 CB  CYS  237      27.334 22.413  1.130 1.00 35.18      B1
ATOM  1601 SG  CYS  237      26.409 22.880 -0.365 1.00 36.40      B1
ATOM  1602 N   ALA  238      29.571 19.804  0.074 1.00 37.29      B1
ATOM  1603 H   ALA  238      29.324 20.158  0.591 1.00 0.00       B1
ATOM  1604 CA  ALA  238      28.841 18.973 -1.090 1.00 36.80      B1
ATOM  1605 CB  ALA  238      30.274 18.684 -1.403 1.00 37.35      B1
ATOM  1606 C   ALA  238      28.320 17.617 -0.911 1.00 36.45      B1
ATOM  1607 O   ALA  238      27.645 17.198 -1.809 1.00 36.54      B1
ATOM  1608 N   THR  239      28.628 16.969  0.193 1.00 38.80      B1
ATOM  1609 H   THR  239      29.236 17.391  0.821 1.00 0.00       B1
ATOM  1610 CA  THR  239      28.158 15.587  0.464 1.00 41.31      B1
ATOM  1611 CB  THR  239      29.158 15.035  1.554 1.00 42.38      B1
ATOM  1612 OG1 THR  239      30.473 15.265  1.031 1.00 45.70      B1
ATOM  1613 HG1 THR  239      31.019 15.668  1.709 1.00 0.00       B1
ATOM  1614 CG2 THR  239      28.936 13.574  1.916 1.00 44.85      B1
ATOM  1615 C   THR  239      26.771 15.341  0.864 1.00 43.94      B1
ATOM  1616 O   THR  239      26.260 14.284  0.460 1.00 43.84      B1
ATOM  1617 N   TYR  240      26.095 16.207  1.669 1.00 40.07      B1
ATOM  1618 H   TYR  240      26.538 17.034  1.953 1.00 0.00       B1
ATOM  1619 CA  TYR  240      24.718 15.992  2.084 1.00 38.21      B1
ATOM  1620 CB  TYR  240      24.594 15.993  3.618 1.00 38.08      B1
ATOM  1621 CG  TYR  240      25.524 14.926  4.193 1.00 43.37      B1
ATOM  1622 CD1 TYR  240      26.475 15.243  5.149 1.00 45.06      B1
ATOM  1623 CE1 TYR  240      27.420 14.283  5.529 1.00 47.35      B1
ATOM  1624 CD2 TYR  240      25.518 13.643  3.641 1.00 43.89      B1
ATOM  1625 CE2 TYR  240      26.442 12.690  4.003 1.00 44.77      B1
ATOM  1626 CZ  TYR  240      27.410 13.005  4.943 1.00 47.96      B1
ATOM  1627 OH  TYR  240      28.390 12.047  5.244 1.00 46.59      B1
ATOM  1628 HH  TYR  240      29.027 11.187  4.992 1.00 0.00       B1
ATOM  1629 C   TYR  240      23.781 17.032  1.516 1.00 39.49      B1
ATOM  1630 O   TYR  240      22.587 16.934  1.775 1.00 42.76      B1
```

FIGURE 5

EP 0 612 846 B1

FIGURE 5

ATOM	1733	C	LEU	251	17.104	22.372	15.493	1.00	42.78	B1
ATOM	1734	O	LEU	251	17.124	21.554	16.395	1.00	45.44	B1
ATOM	1735	N	GLY	252	17.826	23.477	15.610	1.00	44.86	B1
ATOM	1736	H	GLY	252	17.750	24.160	14.910	1.00	0.00	B1
ATOM	1737	CA	GLY	252	18.734	23.711	16.719	1.00	46.68	B1
ATOM	1738	C	GLY	252	18.071	23.596	18.067	1.00	49.18	B1
ATOM	1739	O	GLY	252	18.709	23.318	19.077	1.00	49.23	B1
ATOM	1740	N	HIS	253	16.756	23.787	18.046	1.00	53.74	B1
ATOM	1741	H	HIS	253	16.358	24.055	17.190	1.00	0.00	B1
ATOM	1742	CA	HIS	253	15.859	23.649	19.197	1.00	57.46	B1
ATOM	1743	CB	HIS	253	14.468	24.157	18.764	1.00	62.93	B1
ATOM	1744	CG	HIS	253	13.212	23.813	19.577	1.00	68.75	B1
ATOM	1745	CD2	HIS	253	12.031	24.529	19.414	1.00	71.00	B1
ATOM	1746	ND1	HIS	253	12.980	22.854	20.479	1.00	70.67	B1
ATOM	1747	HD1	HIS	253	13.627	22.193	20.830	1.00	0.00	B1
ATOM	1748	CE1	HIS	253	11.723	22.966	20.845	1.00	73.40	B1
ATOM	1749	NE2	HIS	253	11.156	23.973	20.204	1.00	72.91	B1
ATOM	1750	HE2	HIS	253	10.218	24.260	20.311	1.00	0.00	B1
ATOM	1751	C	HIS	253	15.771	22.209	19.691	1.00	56.06	B1
ATOM	1752	O	HIS	253	15.880	21.827	20.857	1.00	56.17	B1
ATOM	1753	N	SER	254	15.395	21.435	18.724	1.00	53.46	B1
ATOM	1754	H	SER	254	15.278	21.783	17.813	1.00	0.00	B1
ATOM	1755	CA	SER	254	15.177	20.034	18.898	1.00	52.61	B1
ATOM	1756	CB	SER	254	14.613	19.595	17.576	1.00	53.04	B1
ATOM	1757	OG	SER	254	13.793	20.686	17.158	1.00	56.04	B1
ATOM	1758	HG	SER	254	13.369	20.467	16.319	1.00	0.00	B1
ATOM	1759	C	SER	254	16.512	19.386	19.275	1.00	51.48	B1
ATOM	1760	O	SER	254	16.596	18.639	20.245	1.00	51.90	B1
ATOM	1761	N	LEU	255	17.577	19.790	18.562	1.00	49.31	B1
ATOM	1762	H	LEU	255	17.430	20.480	17.889	1.00	0.00	B1
ATOM	1763	CA	LEU	255	18.913	19.272	18.723	1.00	46.02	B1
ATOM	1764	CB	LEU	255	19.706	19.723	17.537	1.00	44.66	B1
ATOM	1765	CG	LEU	255	19.362	18.968	16.274	1.00	44.51	B1
ATOM	1766	CD1	LEU	255	19.810	19.679	15.006	1.00	43.16	B1
ATOM	1767	CD2	LEU	255	19.969	17.604	16.456	1.00	44.67	B1
ATOM	1768	C	LEU	255	19.536	19.718	20.012	1.00	46.56	B1
ATOM	1769	O	LEU	255	20.565	19.174	20.440	1.00	46.82	B1
ATOM	1770	N	GLY	256	18.918	20.759	20.581	1.00	45.93	B1
ATOM	1771	H	GLY	256	18.210	21.225	20.101	1.00	0.00	B1
ATOM	1772	CA	GLY	256	19.277	21.273	21.890	1.00	46.68	B1
ATOM	1773	C	GLY	256	20.669	21.866	21.970	1.00	47.28	B1
ATOM	1774	O	GLY	256	21.273	21.844	23.056	1.00	49.64	B1
ATOM	1775	N	ILE	257	21.143	22.441	20.849	1.00	45.74	B1
ATOM	1776	H	ILE	257	20.497	22.589	20.128	1.00	0.00	B1
ATOM	1777	CA	ILE	257	22.481	23.017	20.726	1.00	43.64	B1
ATOM	1778	CB	ILE	257	22.684	23.363	19.257	1.00	42.54	B1
ATOM	1779	CG2	ILE	257	23.988	24.110	19.073	1.00	41.05	B1
ATOM	1780	CG1	ILE	257	22.694	22.088	18.437	1.00	40.55	B1
ATOM	1781	CD	ILE	257	22.452	22.468	16.970	1.00	39.49	B1
ATOM	1782	C	ILE	257	22.559	24.246	21.616	1.00	43.27	B1
ATOM	1783	O	ILE	257	21.706	25.110	21.450	1.00	43.22	B1
ATOM	1784	N	PRO	258	23.441	24.392	22.608	1.00	43.05	B1
ATOM	1785	CD	PRO	258	24.133	23.321	23.296	1.00	43.29	B1
ATOM	1786	CA	PRO	258	23.559	25.616	23.360	1.00	43.82	B1
ATOM	1787	CB	PRO	258	24.295	25.236	24.612	1.00	41.97	B1
ATOM	1788	CG	PRO	258	25.107	24.064	24.186	1.00	43.79	B1
ATOM	1789	C	PRO	258	24.252	26.703	22.555	1.00	46.06	B1
ATOM	1790	O	PRO	258	24.983	26.513	21.560	1.00	46.59	B1
ATOM	1791	N	TRP	259	23.996	27.887	23.106	1.00	46.75	B1
ATOM	1792	H	TRP	259	23.588	27.921	23.994	1.00	0.00	B1
ATOM	1793	CA	TRP	259	24.427	29.143	22.517	1.00	45.77	B1
ATOM	1794	CB	TRP	259	23.213	30.071	22.397	1.00	46.60	B1
ATOM	1795	CG	TRP	259	23.556	31.372	21.749	1.00	47.51	B1
ATOM	1796	CD2	TRP	259	23.860	31.525	20.430	1.00	47.83	B1
ATOM	1797	CE2	TRP	259	24.154	32.888	20.392	1.00	48.47	B1
ATOM	1798	CE3	TRP	259	23.940	30.745	19.290	1.00	47.39	B1
ATOM	1799	CD1	TRP	259	23.639	32.520	22.493	1.00	48.60	B1
ATOM	1800	NE1	TRP	259	24.013	33.421	21.628	1.00	48.27	B1
ATOM	1801	HE1	TRP	259	24.224	34.344	21.870	1.00	0.00	B1
ATOM	1802	CZ2	TRP	259	24.531	33.486	19.195	1.00	47.40	B1
ATOM	1803	CZ3	TRP	259	24.317	31.344	18.097	1.00	49.07	B1
ATOM	1804	CH2	TRP	259	24.613	32.706	18.050	1.00	49.12	B1
ATOM	1805	C	TRP	259	25.459	29.727	23.440	1.00	44.01	B1
ATOM	1806	O	TRP	259	25.340	29.664	24.671	1.00	43.25	B1
ATOM	1807	N	ALA	260	26.469	30.247	22.777	1.00	43.01	B1
ATOM	1808	H	ALA	260	26.523	30.198	21.796	1.00	0.00	B1
ATOM	1809	CA	ALA	260	27.493	30.973	23.482	1.00	43.48	B1
ATOM	1810	CB	ALA	260	28.874	30.549	22.969	1.00	43.33	B1
ATOM	1811	C	ALA	260	27.249	32.486	23.216	1.00	43.41	B1
ATOM	1812	O	ALA	260	27.315	32.946	22.054	1.00	40.55	B1
ATOM	1813	N	PRO	261	26.853	33.267	24.253	1.00	42.61	B1
ATOM	1814	CD	PRO	261	26.527	32.807	25.606	1.00	42.33	B1
ATOM	1815	CA	PRO	261	26.720	34.701	24.199	1.00	42.37	B1
ATOM	1816	CB	PRO	261	25.778	34.987	25.335	1.00	41.46	B1
ATOM	1817	CG	PRO	261	26.251	34.060	26.411	1.00	40.00	B1
ATOM	1818	C	PRO	261	28.087	35.369	24.311	1.00	42.22	B1
ATOM	1819	O	PRO	261	28.988	34.956	25.037	1.00	38.82	B1
ATOM	1820	N	LEU	262	28.234	36.403	23.486	1.00	45.20	B1
ATOM	1821	H	LEU	262	27.513	36.610	22.853	1.00	0.00	B1
ATOM	1822	CA	LEU	262	29.434	37.210	23.498	1.00	46.50	B1
ATOM	1823	CB	LEU	262	30.531	36.609	22.610	1.00	45.09	B1
ATOM	1824	CG	LEU	262	31.903	37.157	22.964	1.00	42.55	B1
ATOM	1825	CD1	LEU	262	32.344	36.695	24.338	1.00	41.52	B1
ATOM	1826	CD2	LEU	262	32.850	36.730	21.900	1.00	44.21	B1
ATOM	1827	C	LEU	262	29.154	38.628	23.035	1.00	48.56	B1
ATOM	1828	O	LEU	262	29.633	39.470	23.790	1.00	48.23	B1
ATOM	1829	N	SER	263	28.388	38.956	21.960	1.00	51.33	B1
ATOM	1830	H	SER	263	27.982	38.242	21.427	1.00	0.00	B1
ATOM	1831	CA	SER	263	28.127	40.339	21.494	1.00	55.19	B1
ATOM	1832	CB	SER	263	26.871	40.511	20.612	1.00	57.17	B1
ATOM	1833	OG	SER	263	26.498	39.411	19.776	1.00	64.12	B1
ATOM	1834	HG	SER	263	26.093	38.741	20.336	1.00	0.00	B1

FIGURE 5

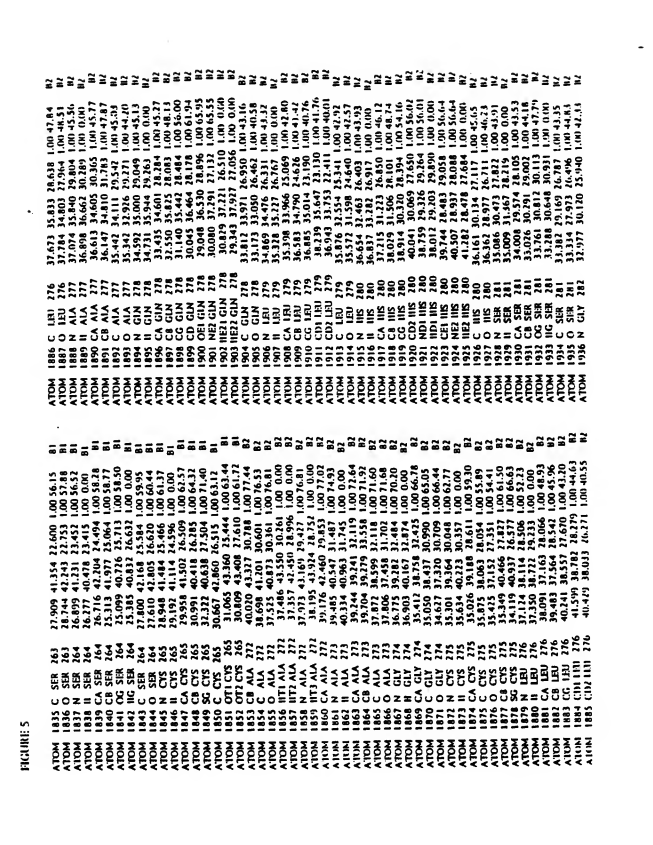


FIGURE 5

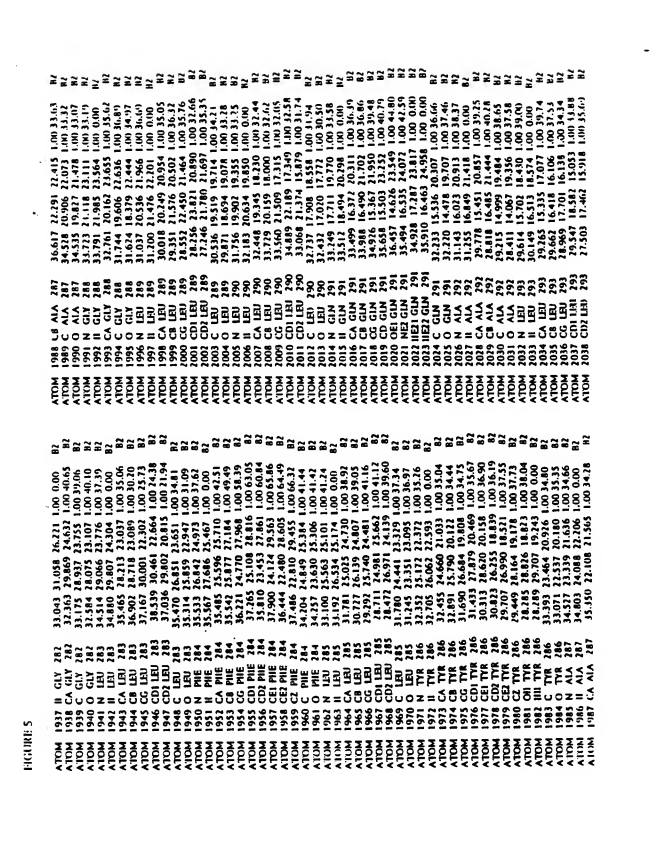


FIGURE 5

FIGURE 5

```
ATOM  2141  H  THR  306      40.469  17.875  12.230  1.00  0.00      B2
ATOM  2142  CA THR  306      41.553  19.633  12.751  1.00  24.39     B2
ATOM  2143  C8 THR  306      41.665  19.931  11.318  1.00  24.58     B2
ATOM  2144  OG1 THR  306     42.074  18.753  10.665  1.00  25.13     B2
ATOM  2145  HG1 THR  306     41.447  18.029  10.768  1.00  0.00      B2
ATOM  2146  CG2 THR  306     42.690  21.027  11.089  1.00  25.77     B2
ATOM  2147  C  THR  306      40.893  20.844  13.419  1.00  25.74     B2
ATOM  2148  O  THR  306      41.488  21.472  14.296  1.00  27.24     B2
ATOM  2149  N  LEU  307      39.615  21.134  13.139  1.00  25.91     B2
ATOM  2150  H  LEU  307      39.125  20.547  12.520  1.00  0.00      B2
ATOM  2151  CA LEU  307     38.900  22.228  13.764  1.00  25.53     B2
ATOM  2152  C8 LEU  307     37.571  22.170  13.142  1.00  25.09     B2
ATOM  2153  CG  LEU  307    36.530  23.097  13.588  1.00  27.93     B2
ATOM  2154  CD1 LEU  307    37.008  24.515  13.484  1.00  29.87     B2
ATOM  2155  CD2 LEU  307    35.311  22.846  12.728  1.00  28.93     B2
ATOM  2156  C  LEU  307      38.850  22.214  15.269  1.00  27.09     B2
ATOM  2157  O  LEU  307      38.854  23.253  15.925  1.00  30.03     B2
ATOM  2158  N  GLN  308      38.875  21.044  15.879  1.00  29.09     B2
ATOM  2159  H  GLN  308      38.883  20.239  15.319  1.00  0.00      B2
ATOM  2160  CA GLN  308     38.824  20.848  17.340  1.00  29.36     B2
ATOM  2161  C8 GLN  308     38.379  19.399  17.562  1.00  29.41     B2
ATOM  2162  CG  GLN  308     37.862  19.140  18.935  1.00  32.24     B2
ATOM  2163  CD  GLN  308     37.586  17.672  19.165  1.00  34.03     B2
ATOM  2164  OE1 GLN  308     36.973  17.023  18.311  1.00  33.48     B2
ATOM  2165  NE2 GLN  308     38.053  17.127  20.299  1.00  31.67     B2
ATOM  2166  HE21 GLN  308    38.547  17.697  20.917  1.00  0.00      B2
ATOM  2167  HE22 GLN  308    37.875  16.174  20.436  1.00  0.00      B2
ATOM  2168  C  GLN  308      40.154  21.138  18.051  1.00  28.94     B2
ATOM  2169  O  GLN  308      40.196  21.796  19.101  1.00  28.44     B2
ATOM  2170  N  LEU  309      41.269  20.610  17.460  1.00  28.78     B2
ATOM  2171  H  LEU  309      41.157  20.120  16.655  1.00  0.00      B2
ATOM  2172  CA LEU  309     42.632  20.923  17.967  1.00  28.56     B2
ATOM  2173  C8 LEU  309     43.671  20.154  17.106  1.00  28.54     B2
ATOM  2174  CG  LEU  309    43.632  18.636  17.241  1.00  24.98     B2
ATOM  2175  CD1 LEU  309    44.595  17.935  16.353  1.00  24.17     B2
ATOM  2176  CD2 LEU  309    43.992  18.310  18.621  1.00  23.45     B2
ATOM  2177  C  LEU  309      42.893  22.416  17.909  1.00  28.74     B2
ATOM  2178  O  LEU  309      43.370  22.957  18.907  1.00  30.32     B2
ATOM  2179  N  ASP  310      42.548  23.027  16.749  1.00  26.58     B2
ATOM  2180  H  ASP  310      42.296  22.437  16.007  1.00  0.00      B2
ATOM  2181  CA ASP  310     42.495  24.447  16.495  1.00  27.90     B2
ATOM  2182  C8 ASP  310     42.015  24.659  15.076  1.00  28.41     B2
ATOM  2183  CG  ASP  310     43.162  24.556  14.096  1.00  31.84     B2
ATOM  2184  OD1 ASP  310     42.959  24.766  12.905  1.00  31.54     B2
ATOM  2185  OD2 ASP  310     44.297  24.314  14.514  1.00  37.32     B2
ATOM  2186  C  ASP  310      41.666  25.410  17.422  1.00  27.99     B2
ATOM  2187  O  ASP  310      42.219  26.429  17.876  1.00  27.23     B2
ATOM  2188  N  VAL  311      40.374  25.086  17.725  1.00  26.29     B2
ATOM  2189  H  VAL  311      39.961  24.347  17.225  1.00  0.00      B2
ATOM  2190  CA VAL  311     39.546  25.803  18.706  1.00  24.29     B2
ATOM  2191  C8 VAL  311      38.098  25.217  18.869  1.00  21.47     B2
ATOM  2192  CG1 VAL  311     37.341  25.915  19.949  1.00  19.01     B2
ATOM  2193  CG2 VAL  311     37.761  25.488  17.667  1.00  18.56     B2
ATOM  2194  C  VAL  311      40.270  25.638  20.020  1.00  27.21     B2
ATOM  2195  O  VAL  311      40.437  26.647  20.719  1.00  29.71     B2
ATOM  2196  N  ALA  312      40.762  24.428  20.357  1.00  27.97     B2
ATOM  2197  H  ALA  312      40.585  23.674  19.756  1.00  0.00      B2
ATOM  2198  CA ALA  312     41.515  24.157  21.583  1.00  29.26     B2
ATOM  2199  C8 ALA  312     41.855  22.688  21.522  1.00  30.53     B2
ATOM  2200  C  ALA  312      42.778  25.026  21.784  1.00  30.06     B2
ATOM  2201  O  ALA  312      43.057  25.508  22.886  1.00  30.04     B2
ATOM  2202  N  ASP  313      43.554  25.286  20.735  1.00  31.43     B2
ATOM  2203  H  ASP  313      43.433  24.730  19.935  1.00  0.00      B2
ATOM  2204  CA ASP  313     44.610  26.275  20.743  1.00  34.22     B2
ATOM  2205  C8 ASP  313     45.279  26.512  19.447  1.00  38.87     B2
ATOM  2206  CG  ASP  313     46.071  25.404  18.866  1.00  44.55     B2
ATOM  2207  OD1 ASP  313     46.225  25.439  17.636  1.00  48.57     B2
ATOM  2208  OD2 ASP  313     46.521  24.553  19.647  1.00  49.25     B2
ATOM  2209  C  ASP  313      44.187  27.699  21.059  1.00  35.17     B2
ATOM  2210  O  ASP  313      44.807  28.390  21.894  1.00  38.60     B2
ATOM  2211  N  PHE  314      43.192  28.216  20.319  1.00  33.36     B2
ATOM  2212  H  PHE  314      42.784  27.683  19.619  1.00  0.00      B2
ATOM  2213  CA PHE  314     42.715  29.548  20.600  1.00  31.09     B2
ATOM  2214  C8 PHE  314     41.572  29.860  19.631  1.00  32.06     B2
ATOM  2215  CG  PHE  314     41.074  31.303  19.636  1.00  33.57     B2
ATOM  2216  CD1 PHE  314     39.780  31.568  19.247  1.00  31.81     B2
ATOM  2217  CD2 PHE  314     41.907  32.354  20.021  1.00  35.05     B2
ATOM  2218  CE1 PHE  314     39.318  32.857  19.240  1.00  29.15     B2
ATOM  2219  CE2 PHE  314     41.453  33.648  20.013  1.00  32.48     B2
ATOM  2220  CZ  PHE  314     40.154  33.870  19.622  1.00  31.81     B2
ATOM  2221  C  PHE  314      42.282  29.601  22.057  1.00  29.90     B2
ATOM  2222  O  PHE  314      42.658  30.550  22.764  1.00  26.82     B2
ATOM  2223  N  ALA  315      41.686  28.537  22.584  1.00  29.29     B2
ATOM  2224  H  ALA  315      41.448  27.764  22.022  1.00  0.00      B2
ATOM  2225  CA ALA  315     41.300  28.583  23.961  1.00  31.61     B2
ATOM  2226  C8 ALA  315     40.632  27.358  24.451  1.00  32.23     B2
ATOM  2227  C  ALA  315      42.482  28.751  24.836  1.00  34.41     B2
ATOM  2228  O  ALA  315      42.361  29.437  25.853  1.00  37.66     B2
ATOM  2229  N  THR  316      43.646  28.250  24.476  1.00  36.16     B2
ATOM  2230  H  THR  316      43.745  27.778  23.625  1.00  0.00      B2
ATOM  2231  CA THR  316     44.780  28.388  25.374  1.00  37.99     B2
ATOM  2232  C8 THR  316     45.795  27.255  25.156  1.00  41.16     B2
ATOM  2233  OG1 THR  316     45.049  26.081  25.521  1.00  45.50     B2
ATOM  2234  HG1 THR  316     44.316  25.900  24.913  1.00  0.00      B2
ATOM  2235  CG2 THR  316     47.152  27.415  25.888  1.00  40.31     B2
ATOM  2236  C  THR  316      45.458  29.710  25.177  1.00  38.47     B2
ATOM  2237  O  THR  316      45.903  30.189  26.247  1.00  39.63     B2
ATOM  2238  N  THR  317      45.620  30.287  23.970  1.00  36.51     B2
ATOM  2239  H  THR  317      45.351  29.800  23.164  1.00  0.00      B2
ATOM  2240  CA THR  317     46.092  31.657  23.844  1.00  37.07     B2
ATOM  2241  C8 THR  317      45.866  32.098  22.392  1.00  36.01     B2
ATOM  2242  OG1 THR  317     46.752  31.352  21.575  1.00  35.31     B2
```

FIGURE 5

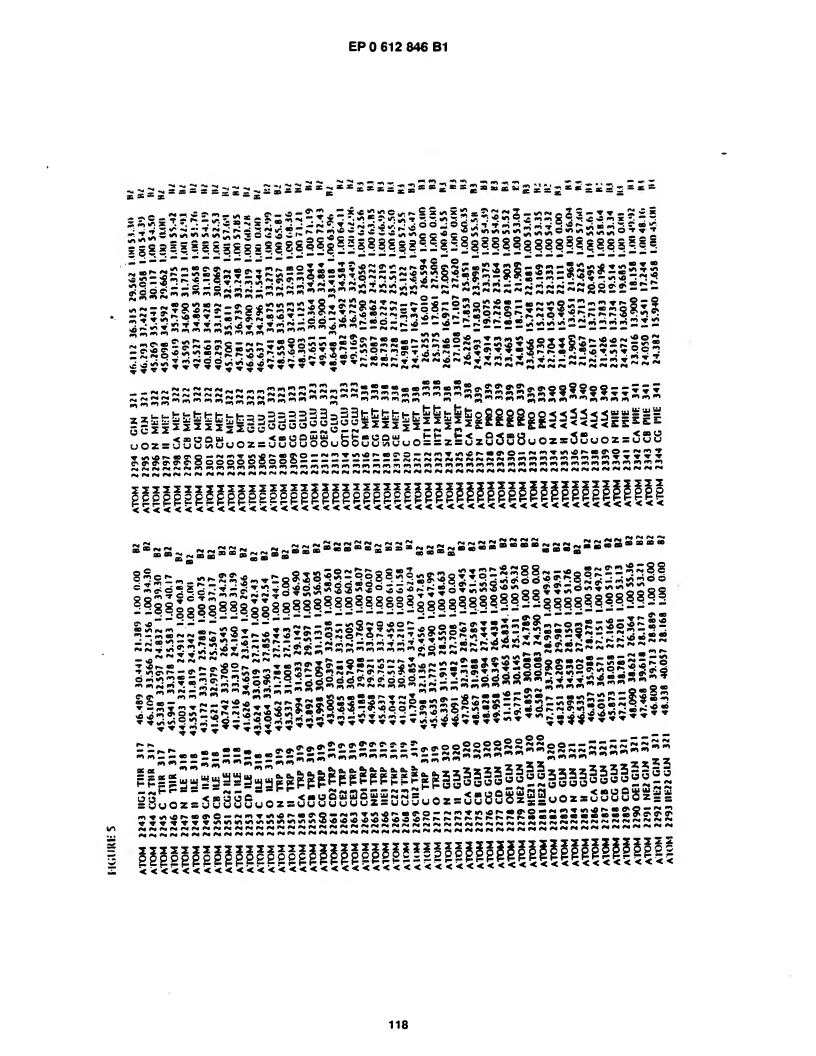
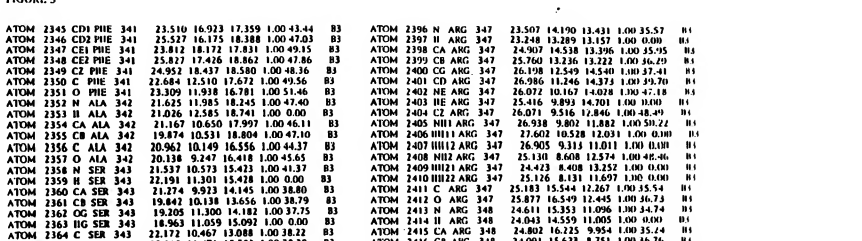


FIGURE 5



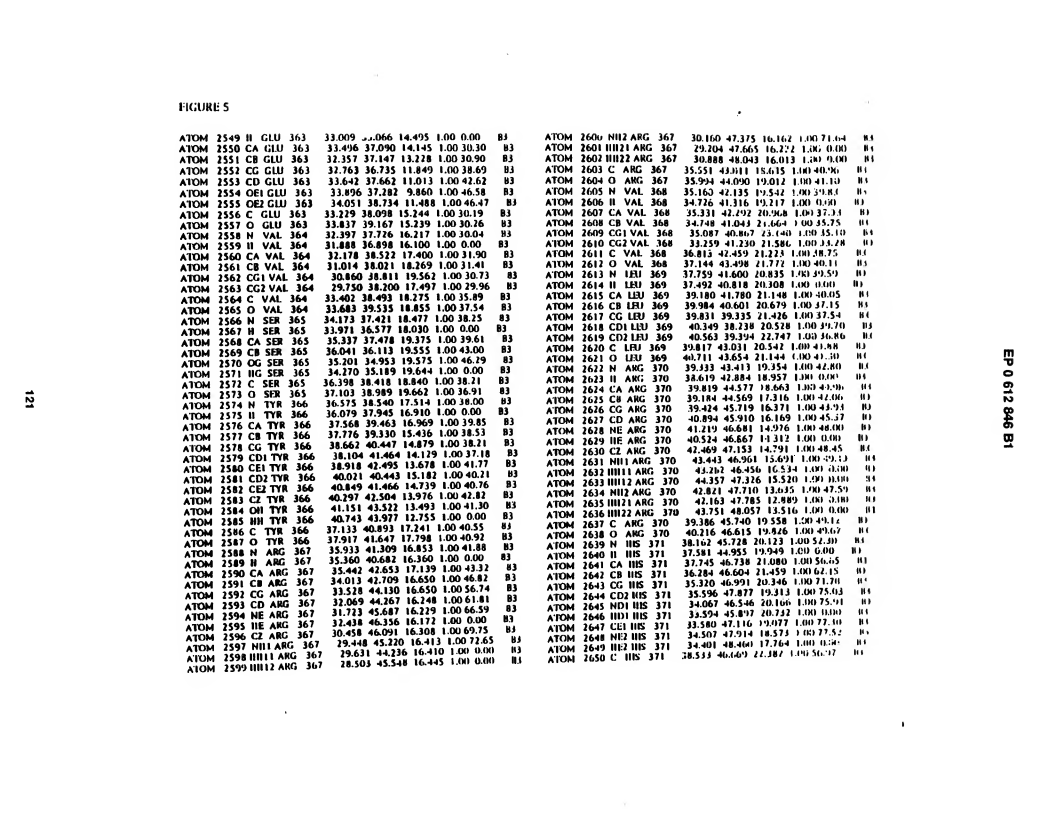
ATOM 2345 CD1 PHE 341 23.510 16.923 17.359 1.00 43.44 B3
ATOM 2346 CD2 PHE 341 25.527 16.175 18.388 1.00 47.03 B3
ATOM 2347 CE1 PHE 341 23.812 18.172 17.831 1.00 49.15 B3
ATOM 2348 CE2 PHE 341 25.827 17.426 18.862 1.00 47.86 B3
ATOM 2349 CZ PHE 341 24.952 18.437 18.580 1.00 48.36 B3
ATOM 2350 C PHE 341 22.684 12.510 17.672 1.00 49.56 B3
ATOM 2351 O PHE 341 23.309 11.938 16.781 1.00 51.46 B3
ATOM 2352 N ALA 342 21.625 11.985 18.245 1.00 47.40 B3
ATOM 2353 H ALA 342 21.026 12.585 18.741 1.00 0.00 B3
ATOM 2354 CA ALA 342 21.167 10.650 17.997 1.00 46.11 B3
ATOM 2355 CB ALA 342 19.874 10.531 18.804 1.00 45.40 B3
ATOM 2356 C ALA 342 20.962 10.149 16.556 1.00 44.37 B3
ATOM 2357 O ALA 342 20.138 9.247 16.418 1.00 45.65 B3
ATOM 2358 N SER 343 21.537 10.573 15.423 1.00 41.37 B3
ATOM 2359 H SER 343 22.191 11.301 15.428 1.00 0.00 B3
ATOM 2360 CA SER 343 21.274 9.973 14.145 1.00 38.80 B3
ATOM 2361 CB SER 343 19.847 10.138 13.656 1.00 38.79 B3
ATOM 2362 OG SER 343 19.205 11.300 14.182 1.00 37.75 B3
ATOM 2363 HG SER 343 18.963 11.059 15.092 1.00 0.00 B3
ATOM 2364 C SER 343 22.172 10.467 13.008 1.00 38.22 B3
ATOM 2365 O SER 343 22.810 11.471 13.382 1.00 38.30 B3
ATOM 2366 N ALA 344 22.206 9.845 11.888 1.00 36.73 B3
ATOM 2367 H ALA 344 21.762 8.978 11.805 1.00 0.00 B3
ATOM 2368 CA ALA 344 22.914 10.384 10.715 1.00 38.09 B3
ATOM 2369 CB ALA 344 22.583 9.640 9.422 1.00 36.78 B3
ATOM 2370 C ALA 344 22.472 11.842 10.496 1.00 37.72 B3
ATOM 2371 O ALA 344 23.271 12.765 10.676 1.00 38.42 B3
ATOM 2372 N PHE 345 21.194 12.042 10.163 1.00 36.10 B3
ATOM 2373 H PHE 345 20.668 11.298 9.811 1.00 0.00 B3
ATOM 2374 CA PHE 345 20.564 13.338 10.195 1.00 34.69 B3
ATOM 2375 CB PHE 345 19.040 13.254 10.128 1.00 33.24 B3
ATOM 2376 CG PHE 345 18.462 14.656 9.918 1.00 32.53 B3
ATOM 2377 CD1 PHE 345 17.715 15.223 10.905 1.00 26.64 B3
ATOM 2378 CD2 PHE 345 18.767 15.343 8.745 1.00 29.99 B3
ATOM 2379 CE1 PHE 345 17.284 16.503 10.682 1.00 33.56 B3
ATOM 2380 CE2 PHE 345 18.333 16.619 8.537 1.00 30.81 B3
ATOM 2381 CZ PHE 345 17.581 17.201 9.520 1.00 31.44 B3
ATOM 2382 C PHE 345 20.888 14.145 11.458 1.00 35.02 B3
ATOM 2383 O PHE 345 21.246 15.319 11.292 1.00 37.81 B3
ATOM 2384 N GLN 346 20.814 13.688 12.691 1.00 32.53 B3
ATOM 2385 H GLN 346 20.516 12.778 12.894 1.00 0.00 B3
ATOM 2386 CA GLN 346 21.156 14.586 13.758 1.00 33.46 B3
ATOM 2387 CB GLN 346 20.899 13.985 15.061 1.00 33.80 B3
ATOM 2388 CG GLN 346 19.459 14.284 15.574 1.00 35.68 B3
ATOM 2389 CD GLN 346 18.788 13.658 16.344 1.00 38.48 B3
ATOM 2390 OE1 GLN 346 19.358 13.328 17.374 1.00 41.78 B3
ATOM 2391 NE2 GLN 346 17.508 13.463 16.167 1.00 41.08 B3
ATOM 2392 HE21 GLN 346 17.088 13.724 15.323 1.00 0.00 B3
ATOM 2393 HE22 GLN 346 17.026 13.063 16.919 1.00 0.00 B3
ATOM 2394 C GLN 346 22.564 15.051 13.773 1.00 35.73 B3
ATOM 2395 O GLN 346 22.766 16.231 14.051 1.00 38.18 B3
ATOM 2396 N ARG 347 23.507 14.190 13.431 1.00 35.57 B3
ATOM 2397 H ARG 347 23.248 13.289 13.157 1.00 0.00 B3
ATOM 2398 CA ARG 347 24.907 14.538 13.396 1.00 35.95 B3
ATOM 2399 CB ARG 347 25.760 13.236 13.222 1.00 36.29 B3
ATOM 2400 CG ARG 347 26.198 12.549 14.540 1.00 37.41 B3
ATOM 2401 CD ARG 347 26.986 11.246 14.373 1.00 39.70 B3
ATOM 2402 NE ARG 347 26.072 10.167 14.028 1.00 47.18 B3
ATOM 2403 HE ARG 347 25.416 9.893 14.701 1.00 0.00 B3
ATOM 2404 CZ ARG 347 26.071 9.516 12.846 1.00 48.49 B3
ATOM 2405 NH1 ARG 347 26.938 9.802 11.882 1.00 50.22 B3
ATOM 2406 HH11 ARG 347 27.602 10.528 12.038 1.00 0.00 B3
ATOM 2407 HH12 ARG 347 26.905 9.313 11.011 1.00 0.00 B3
ATOM 2408 NH2 ARG 347 25.130 8.608 12.574 1.00 48.46 B3
ATOM 2409 HH21 ARG 347 24.423 8.408 13.252 1.00 0.00 B3
ATOM 2410 HH22 ARG 347 25.126 8.131 11.697 1.00 0.00 B3
ATOM 2411 C ARG 347 25.183 15.544 12.267 1.00 35.54 B3
ATOM 2412 O ARG 347 25.877 16.549 12.445 1.00 36.73 B3
ATOM 2413 N ARG 348 24.611 15.351 11.096 1.00 34.74 B3
ATOM 2414 H ARG 348 24.043 14.559 11.005 1.00 0.00 B3
ATOM 2415 CA ARG 348 24.802 16.225 9.954 1.00 35.24 B3
ATOM 2416 CB ARG 348 24.091 15.623 8.751 1.00 36.76 B3
ATOM 2417 CG ARG 348 24.778 14.303 8.450 1.00 44.22 B3
ATOM 2418 CD ARG 348 24.014 13.579 7.329 1.00 49.23 B3
ATOM 2419 NE ARG 348 24.705 12.090 7.457 1.00 54.27 B3
ATOM 2420 HE ARG 348 25.300 11.836 8.193 1.00 0.00 B3
ATOM 2421 CZ ARG 348 24.557 11.226 6.430 1.00 53.75 B3
ATOM 2422 NH1 ARG 348 23.758 11.479 5.381 1.00 51.85 B3
ATOM 2423 HH11 ARG 348 23.234 12.329 5.339 1.00 0.00 B3
ATOM 2424 HH12 ARG 348 23.680 10.807 4.645 1.00 0.00 B3
ATOM 2425 NH2 ARG 348 25.252 10.083 6.462 1.00 54.51 B3
ATOM 2426 HH21 ARG 348 25.169 9.424 5.714 1.00 0.00 B3
ATOM 2427 HH22 ARG 348 25.860 9.894 7.237 1.00 0.00 B3
ATOM 2428 C ARG 348 24.283 17.629 10.237 1.00 34.80 B3
ATOM 2429 O ARG 348 25.078 18.564 10.219 1.00 35.16 B3
ATOM 2430 N ALA 349 23.008 17.795 10.607 1.00 33.85 B3
ATOM 2431 H ALA 349 22.470 16.984 10.755 1.00 0.00 B3
ATOM 2432 CA ALA 349 22.352 19.083 10.853 1.00 32.96 B3
ATOM 2433 CB ALA 349 20.809 18.894 11.070 1.00 33.16 B3
ATOM 2434 C ALA 349 22.945 19.746 12.083 1.00 31.84 B3
ATOM 2435 O ALA 349 22.981 20.969 12.210 1.00 30.69 B3
ATOM 2436 N GLY 350 23.444 18.954 13.018 1.00 31.30 B3
ATOM 2437 H GLY 350 23.308 17.984 12.976 1.00 0.00 B3
ATOM 2438 CA GLY 350 24.117 19.505 14.181 1.00 31.08 B3
ATOM 2439 C GLY 350 25.462 20.025 13.753 1.00 30.79 B3
ATOM 2440 O GLY 350 25.974 21.010 14.280 1.00 31.38 B3
ATOM 2441 N GLY 351 25.991 19.374 12.731 1.00 30.03 B3
ATOM 2442 H GLY 351 25.546 18.582 12.367 1.00 0.00 B3
ATOM 2443 CA GLY 351 27.263 19.735 12.184 1.00 29.95 B3
ATOM 2444 C GLY 351 27.182 21.097 11.534 1.00 29.25 B3
ATOM 2445 O GLY 351 27.937 21.974 11.919 1.00 28.73 B3
ATOM 2446 N VAL 352 26.356 21.285 10.522 1.00 28.92 B3

FIGURE 5

```
ATOM  2447 H   VAL  352      25.859  40.484  10.214  1.00  0.00      B3
ATOM  2448 CA  VAL  352      26.079  22.567   9.881  1.00 28.59      B3
ATOM  2449 CB  VAL  352      24.845  22.452   9.004  1.00 28.96      B3
ATOM  2450 CG1 VAL  352      24.627  23.785   8.346  1.00 30.86      B3
ATOM  2451 CG2 VAL  352      25.021  21.475   7.875  1.00 26.94      B3
ATOM  2452 C   VAL  352      25.849  23.709  10.890  1.00 29.29      B3
ATOM  2453 O   VAL  352      26.520  24.747  10.853  1.00 31.02      B3
ATOM  2454 N   LEU  353      24.923  23.543  11.819  1.00 27.52      B3
ATOM  2455 H   LEU  353      24.404  22.709  11.838  1.00  0.00      B3
ATOM  2456 CA  LEU  353      24.635  24.548  12.817  1.00 26.18      B3
ATOM  2457 CB  LEU  353      23.434  24.113  13.636  1.00 27.87      B3
ATOM  2458 CG  LEU  353      22.098  24.034  12.931  1.00 26.54      B3
ATOM  2459 CD1 LEU  353      21.064  23.617  13.924  1.00 25.49      B3
ATOM  2460 CD2 LEU  353      21.750  25.372  12.320  1.00 28.23      B3
ATOM  2461 C   LEU  353      25.742  24.905  13.772  1.00 27.17      B3
ATOM  2462 O   LEU  353      25.838  26.093  14.088  1.00 28.00      B3
ATOM  2463 N   VAL  354      26.539  23.949  14.318  1.00 27.20      B3
ATOM  2464 H   VAL  354      26.321  23.006  14.139  1.00  0.00      B3
ATOM  2465 CA  VAL  354      27.712  24.312  15.157  1.00 24.62      B3
ATOM  2466 CB  VAL  354      28.236  22.910  15.745  1.00 22.01      B3
ATOM  2467 CG1 VAL  354      29.568  23.089  16.406  1.00 19.82      B3
ATOM  2468 CG2 VAL  354      27.276  22.467  16.802  1.00 23.96      B3
ATOM  2469 C   VAL  354      28.812  24.895  14.332  1.00 25.46      B3
ATOM  2470 O   VAL  354      29.439  25.832  14.798  1.00 26.23      B3
ATOM  2471 N   ALA  355      29.059  24.530  13.089  1.00 26.12      B3
ATOM  2472 H   ALA  355      28.579  23.745  12.744  1.00  0.00      B3
ATOM  2473 CA  ALA  355      30.025  25.180  12.235  1.00 26.54      B3
ATOM  2474 CB  ALA  355      30.034  24.591  10.869  1.00 22.08      B3
ATOM  2475 C   ALA  355      29.533  26.601  12.096  1.00 28.51      B3
ATOM  2476 O   ALA  355      30.315  27.498  12.344  1.00 31.93      B3
ATOM  2477 N   SER  356      28.271  26.884  11.905  1.00 30.30      B3
ATOM  2478 H   SER  356      27.654  26.134  11.665  1.00  0.00      B3
ATOM  2479 CA  SER  356      27.778  28.249  11.625  1.00 31.10      B3
ATOM  2480 CB  SER  356      26.401  28.147  11.016  1.00 35.23      B3
ATOM  2481 OG  SER  356      25.679  29.380  10.905  1.00 43.82      B3
ATOM  2482 HG  SER  356      26.250  30.004  10.429  1.00  0.00      B3
ATOM  2483 C   SER  356      27.763  29.096  12.901  1.00 29.75      B3
ATOM  2484 O   SER  356      28.115  30.289  12.898  1.00 28.35      B3
ATOM  2485 N   HIS  357      27.465  28.464  14.021  1.00 27.82      B3
ATOM  2486 H   HIS  357      27.301  27.498  14.019  1.00  0.00      B3
ATOM  2487 CA  HIS  357      27.434  29.194  15.259  1.00 26.58      B3
ATOM  2488 CB  HIS  357      26.735  28.365  16.305  1.00 25.77      B3
ATOM  2489 CG  HIS  357      25.219  28.360  16.063  1.00 27.67      B3
ATOM  2490 CD2 HIS  357      24.563  28.767  14.915  1.00 28.94      B3
ATOM  2491 ND1 HIS  357      24.277  27.963  16.915  1.00 28.43      B3
ATOM  2492 HD1 HIS  357      24.456  27.622  17.828  1.00  0.00      B3
ATOM  2493 CE1 HIS  357      23.112  28.103  16.337  1.00 28.64      B3
ATOM  2494 NE2 HIS  357      23.298  28.589  15.130  1.00 29.48      B3
ATOM  2495 HE2 HIS  357      22.576  28.801  14.495  1.00  0.00      B3
ATOM  2496 C   HIS  357      28.857  29.506  15.645  1.00 27.91      B3
ATOM  2497 O   HIS  357      29.119  30.606  16.115  1.00 29.15      B3

ATOM  2498 N   LEU  358      29.830  28.637  15.383  1.00 28.33      B3
ATOM  2499 H   LEU  358      29.624  27.761  14.997  1.00  0.00      B3
ATOM  2500 CA  LEU  358      31.211  28.940  15.721  1.00 26.39      B3
ATOM  2501 CB  LEU  358      32.030  27.702  15.547  1.00 21.42      B3
ATOM  2502 CG  LEU  358      33.457  27.878  15.734  1.00 20.42      B3
ATOM  2503 CD1 LEU  358      33.805  28.078  17.165  1.00 16.79      B3
ATOM  2504 CD2 LEU  358      34.075  26.714  15.072  1.00 22.89      B3
ATOM  2505 C   LEU  358      31.721  30.067  14.822  1.00 26.45      B3
ATOM  2506 O   LEU  358      32.372  30.939  15.378  1.00 27.12      B3
ATOM  2507 N   GLN  359      31.460  30.130  13.518  1.00 26.41      B3
ATOM  2508 H   GLN  359      31.048  29.337  13.114  1.00  0.00      B3
ATOM  2509 CA  GLN  359      31.863  31.254  12.671  1.00 29.10      B3
ATOM  2510 CB  GLN  359      31.204  31.209  11.292  1.00 30.49      B3
ATOM  2511 CG  GLN  359      31.395  29.952  10.455  1.00 38.94      B3
ATOM  2512 CD  GLN  359      32.842  29.636  10.091  1.00 42.89      B3
ATOM  2513 OE1 GLN  359      33.774  29.979  10.821  1.00 46.15      B3
ATOM  2514 NE2 GLN  359      33.103  28.987   8.967  1.00 41.34      B3
ATOM  2515 HE21 GLN  359      32.341  28.706   8.412  1.00  0.00      B3
ATOM  2516 HE22 GLN  359      34.039  28.838   8.740  1.00  0.00      B3
ATOM  2517 C   GLN  359      31.512  32.621  13.254  1.00 29.49      B3
ATOM  2518 O   GLN  359      32.427  33.427  13.484  1.00 30.06      B3
ATOM  2519 N   SER  360      30.201  32.810  13.528  1.00 28.66      B3
ATOM  2520 H   SER  360      29.595  32.061  13.343  1.00  0.00      B3
ATOM  2521 CA  SER  360      29.570  34.003  14.071  1.00 27.35      B3
ATOM  2522 CB  SER  360      28.121  33.761  14.536  1.00 26.70      B3
ATOM  2523 OG  SER  360      27.498  33.539  13.078  1.00 29.72      B3
ATOM  2524 HG  SER  360      26.637  33.112  13.288  1.00  0.00      B3
ATOM  2525 C   SER  360      30.202  34.387  15.353  1.00 27.15      B3
ATOM  2526 O   SER  360      30.575  35.550  15.498  1.00 26.94      B3
ATOM  2527 N   PHE  361      30.381  33.403  16.246  1.00 25.88      B3
ATOM  2528 H   PHE  361      30.055  32.499  16.040  1.00  0.00      B3
ATOM  2529 CA  PHE  361      31.066  33.626  17.517  1.00 25.20      B3
ATOM  2530 CB  PHE  361      31.092  32.335  18.302  1.00 24.30      B3
ATOM  2531 CG  PHE  361      31.796  32.394  19.655  1.00 23.63      B3
ATOM  2532 CD1 PHE  361      31.127  32.854  20.777  1.00 22.44      B3
ATOM  2533 CD2 PHE  361      33.098  31.931  19.770  1.00 23.35      B3
ATOM  2534 CE1 PHE  361      31.772  32.834  22.000  1.00 22.78      B3
ATOM  2535 CE2 PHE  361      33.719  31.921  21.002  1.00 21.26      B3
ATOM  2536 CZ  PHE  361      33.058  32.368  22.114  1.00 19.54      B3
ATOM  2537 C   PHE  361      32.505  34.143  17.385  1.00 26.56      B3
ATOM  2538 O   PHE  361      32.914  34.979  18.183  1.00 26.76      B3
ATOM  2539 N   LEU  362      33.309  33.645  16.441  1.00 28.17      B3
ATOM  2540 H   LEU  362      32.962  32.921  15.874  1.00  0.00      B3
ATOM  2541 CA  LEU  362      34.679  34.089  16.222  1.00 28.89      B3
ATOM  2542 CB  LEU  362      35.452  33.125  15.338  1.00 28.18      B3
ATOM  2543 CG  LEU  362      35.603  31.656  15.781  1.00 29.61      B3
ATOM  2544 CD1 LEU  362      36.306  30.996  14.633  1.00 31.63      B3
ATOM  2545 CD2 LEU  362      36.374  31.433  17.055  1.00 26.38      B3
ATOM  2546 C   LEU  362      34.692  35.449  15.536  1.00 29.18      B3
ATOM  2547 O   LEU  362      35.649  36.202  15.748  1.00 27.41      B3
ATOM  2548 N   GLU  363      33.664  35.763  14.710  1.00 29.54      B3
```

FIGURE 5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ATOM 2551 CB GLU 363 32.357 37.147 13.228 1.00 30.90 BJ
ATOM 2552 CG GLU 363 32.763 36.735 11.849 1.00 38.69 BJ
ATOM 2553 CD GLU 363 33.642 37.662 11.013 1.00 42.62 BJ
ATOM 2554 OE1 GLU 363 33.896 37.282 9.860 1.00 46.58 BJ
ATOM 2555 OE2 GLU 363 34.051 38.734 11.488 1.00 46.47 BJ
ATOM 2556 C GLU 363 33.229 38.098 15.244 1.00 30.19 BJ
ATOM 2557 O GLU 363 33.837 39.167 15.239 1.00 30.26 BJ
ATOM 2558 N VAL 364 32.397 37.726 16.217 1.00 30.04 BJ
ATOM 2559 H VAL 364 31.888 36.898 16.100 1.00 0.00 BJ
ATOM 2560 CA VAL 364 32.178 38.522 17.400 1.00 31.90 BJ
ATOM 2561 CB VAL 364 31.014 38.021 18.269 1.00 31.41 BJ
ATOM 2562 CG1 VAL 364 30.860 38.811 19.562 1.00 30.73 BJ
ATOM 2563 CG2 VAL 364 29.750 38.200 17.497 1.00 29.96 BJ
ATOM 2564 C VAL 364 33.402 38.493 18.275 1.00 35.89 BJ
ATOM 2565 O VAL 364 33.683 39.535 18.855 1.00 37.54 BJ
ATOM 2566 N SER 365 34.173 37.421 18.477 1.00 38.25 BJ
ATOM 2567 H SER 365 33.971 36.577 18.030 1.00 0.00 BJ
ATOM 2568 CA SER 365 35.337 37.478 19.375 1.00 39.61 BJ
ATOM 2569 CB SER 365 36.041 36.113 19.555 1.00 43.00 BJ
ATOM 2570 OG SER 365 35.203 34.953 19.575 1.00 46.29 BJ
ATOM 2571 HG SER 365 34.270 35.189 19.644 1.00 0.00 BJ
ATOM 2572 C SER 365 36.398 38.418 18.840 1.00 38.21 BJ
ATOM 2573 O SER 365 37.103 38.989 19.662 1.00 36.91 BJ
ATOM 2574 N TYR 366 36.575 38.540 17.514 1.00 38.00 BJ
ATOM 2575 H TYR 366 36.079 37.945 16.910 1.00 0.00 BJ
ATOM 2576 CA TYR 366 37.568 39.463 16.969 1.00 39.85 BJ
ATOM 2577 CB TYR 366 37.776 39.330 15.436 1.00 40.53 BJ
ATOM 2578 CG TYR 366 38.662 40.447 14.879 1.00 38.21 BJ
ATOM 2579 CD1 TYR 366 38.104 41.464 14.129 1.00 37.18 BJ
ATOM 2580 CE1 TYR 366 38.918 42.495 13.678 1.00 41.77 BJ
ATOM 2581 CD2 TYR 366 40.021 40.443 15.182 1.00 40.21 BJ
ATOM 2582 CE2 TYR 366 40.849 41.466 14.739 1.00 40.76 BJ
ATOM 2583 CZ TYR 366 40.297 42.504 13.976 1.00 42.82 BJ
ATOM 2584 OH TYR 366 41.151 43.522 13.493 1.00 41.30 BJ
ATOM 2585 HH TYR 366 40.743 43.977 12.755 1.00 0.00 BJ
ATOM 2586 C TYR 366 37.133 40.893 17.241 1.00 40.55 BJ
ATOM 2587 O TYR 366 37.917 41.647 17.798 1.00 40.92 BJ
ATOM 2588 N ARG 367 35.933 41.309 16.853 1.00 41.88 BJ
ATOM 2589 H ARG 367 35.360 40.682 16.360 1.00 0.00 BJ
ATOM 2590 CA ARG 367 35.442 42.653 17.139 1.00 43.32 BJ
ATOM 2591 CB ARG 367 34.013 42.709 16.650 1.00 46.82 BJ
ATOM 2592 CG ARG 367 33.528 44.130 16.650 1.00 56.74 BJ
ATOM 2593 CD ARG 367 32.069 44.267 16.248 1.00 61.81 BJ
ATOM 2594 NE ARG 367 31.723 45.687 16.229 1.00 66.59 BJ
ATOM 2595 HE ARG 367 32.438 46.356 16.172 1.00 0.00 BJ
ATOM 2596 CZ ARG 367 30.458 46.091 16.308 1.00 69.75 BJ
ATOM 2597 NH1 ARG 367 29.448 45.220 16.413 1.00 72.65 BJ
ATOM 2598 HH11 ARG 367 29.631 44.236 16.410 1.00 0.00 BJ
ATOM 2599 HH12 ARG 367 28.503 45.548 16.445 1.00 0.00 BJ
ATOM 2600 NH2 ARG 367 30.160 47.375 16.162 1.00 71.64 BJ
ATOM 2601 HH21 ARG 367 29.204 47.665 16.272 1.00 0.00 BJ
ATOM 2602 HH22 ARG 367 30.888 48.043 16.013 1.00 0.00 BJ
ATOM 2603 C ARG 367 35.551 43.011 18.615 1.00 40.96 BJ
ATOM 2604 O ARG 367 35.994 44.090 19.012 1.00 41.14 BJ
ATOM 2605 N VAL 368 35.163 42.135 19.542 1.00 39.84 BJ
ATOM 2606 H VAL 368 34.726 41.316 19.217 1.00 0.00 BJ
ATOM 2607 CA VAL 368 35.331 42.492 20.968 1.00 37.33 BJ
ATOM 2608 CB VAL 368 34.748 41.043 21.664 1.00 35.75 BJ
ATOM 2609 CG1 VAL 368 35.087 40.867 23.140 1.00 35.10 BJ
ATOM 2610 CG2 VAL 368 33.259 41.230 21.586 1.00 33.28 BJ
ATOM 2611 C VAL 368 36.813 42.459 21.223 1.00 38.75 BJ
ATOM 2612 O VAL 368 37.144 43.498 21.772 1.00 40.11 BJ
ATOM 2613 N LEU 369 37.759 41.600 20.835 1.00 39.59 BJ
ATOM 2614 H LEU 369 37.492 40.818 20.308 1.00 0.00 BJ
ATOM 2615 CA LEU 369 39.180 41.780 21.148 1.00 40.05 BJ
ATOM 2616 CB LEU 369 39.984 40.601 20.679 1.00 37.15 BJ
ATOM 2617 CG LEU 369 39.831 39.335 21.426 1.00 37.54 BJ
ATOM 2618 CD1 LEU 369 40.349 38.238 20.528 1.00 39.70 BJ
ATOM 2619 CD2 LEU 369 40.563 39.394 22.747 1.00 36.86 BJ
ATOM 2620 C LEU 369 39.817 43.031 20.542 1.00 41.46 BJ
ATOM 2621 O LEU 369 40.711 43.654 21.144 1.00 43.30 BJ
ATOM 2622 N ARG 370 39.333 43.413 19.354 1.00 42.80 BJ
ATOM 2623 H ARG 370 38.619 42.884 18.957 1.00 0.00 BJ
ATOM 2624 CA ARG 370 39.819 44.577 18.663 1.00 43.96 BJ
ATOM 2625 CB ARG 370 39.184 44.569 17.316 1.00 42.06 BJ
ATOM 2626 CG ARG 370 39.424 45.719 16.371 1.00 44.94 BJ
ATOM 2627 CD ARG 370 40.894 45.910 16.169 1.00 45.27 BJ
ATOM 2628 NE ARG 370 41.219 46.681 14.976 1.00 48.00 BJ
ATOM 2629 HE ARG 370 40.524 46.667 14.312 1.00 0.00 BJ
ATOM 2630 CZ ARG 370 42.469 47.153 14.791 1.00 48.45 BJ
ATOM 2631 NH1 ARG 370 43.443 46.961 15.691 1.00 50.53 BJ
ATOM 2632 HH11 ARG 370 43.262 46.456 16.534 1.00 0.00 BJ
ATOM 2633 HH12 ARG 370 44.357 47.326 15.520 1.00 0.00 BJ
ATOM 2634 NH2 ARG 370 42.821 47.710 13.635 1.00 47.59 BJ
ATOM 2635 HH21 ARG 370 42.163 47.785 12.889 1.00 0.00 BJ
ATOM 2636 HH22 ARG 370 43.751 48.057 13.516 1.00 0.00 BJ
ATOM 2637 C ARG 370 39.386 45.740 19.558 1.00 45.14 BJ
ATOM 2638 O ARG 370 40.216 46.615 19.846 1.00 45.67 BJ
ATOM 2639 N HIS 371 38.162 45.728 20.123 1.00 45.80 BJ
ATOM 2640 H HIS 371 37.581 44.955 19.949 1.00 0.00 BJ
ATOM 2641 CA HIS 371 37.745 46.738 21.080 1.00 46.65 BJ
ATOM 2642 CB HIS 371 36.284 46.604 21.459 1.00 62.15 BJ
ATOM 2643 CG HIS 371 35.320 46.991 20.346 1.00 71.70 BJ
ATOM 2644 CD2 HIS 371 35.596 47.877 19.313 1.00 75.03 BJ
ATOM 2645 ND1 HIS 371 34.067 46.546 20.166 1.00 75.91 BJ
ATOM 2646 HD1 HIS 371 33.594 45.897 20.722 1.00 0.00 BJ
ATOM 2647 CE1 HIS 371 33.580 47.116 19.077 1.00 77.10 BJ
ATOM 2648 NE2 HIS 371 34.507 47.914 18.573 1.00 77.52 BJ
ATOM 2649 HE2 HIS 371 34.401 48.464 17.764 1.00 0.00 BJ
ATOM 2650 C HIS 371 38.533 46.649 22.387 1.00 50.37 BJ

FIGURE 5

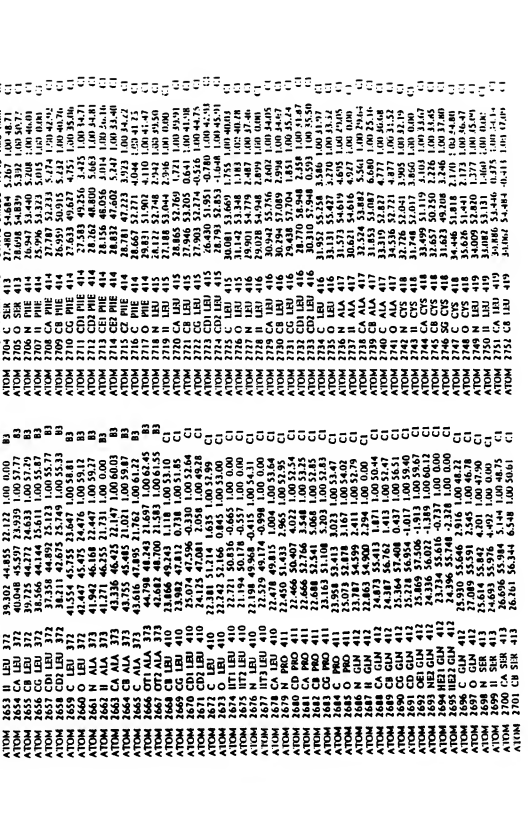

FIGURE 5

FIGURE 5

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ATOM  2855 CA  GLY  429      49.289  -.964   0.029  1.00 25.44      C1
ATOM  2856 C   GLY  429      50.405  48.649  -0.716  1.00 27.39      C1
ATOM  2857 O   GLY  429      51.528  48.135  -0.741  1.00 28.51      C1
ATOM  2858 N   ALA  430      50.127  49.840  -1.271  1.00 28.26      C1
ATOM  2859 H   ALA  430      49.216  50.185  -1.172  1.00  0.00      C1
ATOM  2860 CA  ALA  430      51.094  50.643  -2.015  1.00 26.04      C1
ATOM  2861 CB  ALA  430      50.490  51.976  -2.407  1.00 27.93      C1
ATOM  2862 C   ALA  430      52.300  50.927  -1.133  1.00 25.19      C1
ATOM  2863 O   ALA  430      53.393  51.053  -1.655  1.00 25.43      C1
ATOM  2864 N   ALA  431      52.171  50.979   0.186  1.00 24.05      C1
ATOM  2865 H   ALA  431      51.279  50.872   0.579  1.00  0.00      C1
ATOM  2866 CA  ALA  431      53.295  51.213   1.035  1.00 26.29      C1
ATOM  2867 CB  ALA  431      52.874  51.522   2.458  1.00 24.14      C1
ATOM  2868 C   ALA  431      54.139  49.972   1.073  1.00 29.82      C1
ATOM  2869 O   ALA  431      55.360  50.085   0.959  1.00 31.97      C1
ATOM  2870 N   LEU  432      53.562  48.777   1.203  1.00 31.87      C1
ATOM  2871 H   LEU  432      52.585  48.726   1.279  1.00  0.00      C1
ATOM  2872 CA  LEU  432      54.337  47.540   1.165  1.00 33.92      C1
ATOM  2873 CB  LEU  432      53.430  46.315   1.301  1.00 37.42      C1
ATOM  2874 CG  LEU  432      54.063  44.952   1.574  1.00 37.40      C1
ATOM  2875 CD1 LEU  432      54.751  44.949   2.950  1.00 38.10      C1
ATOM  2876 CD2 LEU  432      52.966  43.901   1.492  1.00 36.27      C1
ATOM  2877 C   LEU  432      55.096  47.404  -0.146  1.00 33.74      C1
ATOM  2878 O   LEU  432      56.306  47.179  -0.138  1.00 33.29      C1
ATOM  2879 N   GLN  433      54.402  47.564  -1.276  1.00 34.57      C1
ATOM  2880 H   GLN  433      53.439  47.733  -1.186  1.00  0.00      C1
ATOM  2881 CA  GLN  433      55.002  47.526  -2.600  1.00 35.83      C1
ATOM  2882 CB  GLN  433      53.999  47.892  -3.664  1.00 35.52      C1
ATOM  2883 CG  GLN  433      52.996  46.823  -3.932  1.00 39.40      C1
ATOM  2884 CD  GLN  433      52.049  47.097  -4.973  1.00 42.46      C1
ATOM  2885 OE1 GLN  433      50.924  47.526  -4.786  1.00 48.22      C1
ATOM  2886 NE2 GLN  433      52.376  46.878  -6.225  1.00 44.72      C1
ATOM  2887 HE21 GLN  433      53.271  46.540  -6.433  1.00  0.00      C1
ATOM  2888 HE22 GLN  433      51.693  47.087  -6.892  1.00  0.00      C1
ATOM  2889 C   GLN  433      56.177  48.485  -2.757  1.00 36.48      C1
ATOM  2890 O   GLN  433      57.214  48.118  -3.311  1.00 38.08      C1
ATOM  2891 N   GLU  434      56.055  49.719  -2.287  1.00 36.11      C1
ATOM  2892 H   GLU  434      55.210  49.978  -1.854  1.00  0.00      C1
ATOM  2893 CA  GLU  434      57.089  50.719  -2.426  1.00 35.93      C1
ATOM  2894 CB  GLU  434      56.408  52.030  -2.068  1.00 41.28      C1
ATOM  2895 CG  GLU  434      57.126  53.356  -2.019  1.00 43.07      C1
ATOM  2896 CD  GLU  434      57.832  53.516  -0.698  1.00 45.70      C1
ATOM  2897 OE1 GLU  434      57.190  53.538   0.367  1.00 49.33      C1
ATOM  2898 OE2 GLU  434      59.051  53.579  -0.760  1.00 45.45      C1
ATOM  2899 C   GLU  434      58.257  50.348  -1.548  1.00 34.00      C1
ATOM  2900 O   GLU  434      59.388  50.481  -1.983  1.00 32.93      C1
ATOM  2901 N   LYS  435      58.067  49.860  -0.330  1.00 34.14      C1
ATOM  2902 H   LYS  435      57.146  49.837   0.014  1.00  0.00      C1
ATOM  2903 CA  LYS  435      59.151  49.358   0.511  1.00 34.56      C1
ATOM  2904 CB  LYS  435      58.577  49.010   1.847  1.00 33.89      C1
ATOM  2905 CG  LYS  435      58.357  50.231   2.709  1.00 36.71      C1
ATOM  2906 CD  LYS  435      58.244  49.748   4.137  1.00 40.31      C1
ATOM  2907 CE  LYS  435      58.293  50.861   5.213  1.00 45.32      C1
ATOM  2908 NZ  LYS  435      58.494  50.325   6.575  1.00 47.31      C1
ATOM  2909 HZ1 LYS  435      59.388  49.795   6.611  1.00  0.00      C1
ATOM  2910 HZ2 LYS  435      57.708  49.689   6.818  1.00  0.00      C1
ATOM  2911 HZ3 LYS  435      58.534  51.109   7.257  1.00  0.00      C1
ATOM  2912 C   LYS  435      59.906  48.135  -0.065  1.00 36.10      C1
ATOM  2913 O   LYS  435      61.139  48.036  -0.012  1.00 37.08      C1
ATOM  2914 N   LEU  436      59.215  47.168  -0.665  1.00 36.28      C1
ATOM  2915 H   LEU  436      58.235  47.245  -0.651  1.00  0.00      C1
ATOM  2916 CA  LEU  436      59.793  45.994  -1.304  1.00 34.25      C1
ATOM  2917 CB  LEU  436      58.655  45.076  -1.753  1.00 34.01      C1
ATOM  2918 CG  LEU  436      57.920  44.327  -0.610  1.00 34.72      C1
ATOM  2919 CD1 LEU  436      56.764  43.538  -1.181  1.00 33.50      C1
ATOM  2920 CD2 LEU  436      58.880  43.375   0.117  1.00 36.39      C1
ATOM  2921 C   LEU  436      60.669  46.383  -2.467  1.00 33.31      C1
ATOM  2922 O   LEU  436      61.756  45.825  -2.647  1.00 33.94      C1
ATOM  2923 N   CYS  437      60.220  47.374  -3.222  1.00 32.34      C1
ATOM  2924 H   CYS  437      59.290  47.661  -3.097  1.00  0.00      C1
ATOM  2925 CA  CYS  437      60.978  47.949  -4.301  1.00 32.01      C1
ATOM  2926 C   CYS  437      62.214  48.704  -3.857  1.00 34.70      C1
ATOM  2927 O   CYS  437      63.313  48.599  -4.412  1.00 36.46      C1
ATOM  2928 CB  CYS  437      60.094  48.840  -5.008  1.00 30.97      C1
ATOM  2929 SG  CYS  437      61.003  49.666  -6.319  1.00 36.42      C1
ATOM  2930 N   ALA  438      62.016  49.463  -2.785  1.00 36.35      C1
ATOM  2931 H   ALA  438      61.108  49.547  -2.431  1.00  0.00      C1
ATOM  2932 CA  ALA  438      63.060  50.326  -2.170  1.00 35.83      C1
ATOM  2933 CB  ALA  438      62.440  51.107  -1.153  1.00 36.38      C1
ATOM  2934 C   ALA  438      64.065  49.294  -1.527  1.00 37.01      C1
ATOM  2935 O   ALA  438      65.132  49.168  -2.092  1.00 39.39      C1
ATOM  2936 N   THR  439      63.808  48.591  -0.422  1.00 36.59      C1
ATOM  2937 H   THR  439      62.947  48.723   0.014  1.00  0.00      C1
ATOM  2938 CA  THR  439      64.742  47.669   0.223  1.00 35.70      C1
ATOM  2939 CB  THR  439      64.073  47.042   1.400  1.00 35.34      C1
ATOM  2940 OG1 THR  439      63.323  48.048   2.040  1.00 35.83      C1
ATOM  2941 HG1 THR  439      62.419  47.999   1.706  1.00  0.00      C1
ATOM  2942 CG2 THR  439      65.039  46.479   2.369  1.00 36.50      C1
ATOM  2943 C   THR  439      65.331  46.517  -0.590  1.00 36.10      C1
ATOM  2944 O   THR  439      66.448  46.093  -0.312  1.00 36.51      C1
ATOM  2945 N   TYR  440      64.603  45.917  -1.548  1.00 36.02      C1
ATOM  2946 H   TYR  440      63.751  46.319  -1.822  1.00  0.00      C1
ATOM  2947 CA  TYR  440      65.057  44.691  -2.198  1.00 34.28      C1
ATOM  2948 CB  TYR  440      64.175  43.480  -1.878  1.00 33.99      C1
ATOM  2949 CG  TYR  440      64.016  43.240  -0.397  1.00 34.64      C1
ATOM  2950 CD1 TYR  440      62.773  43.230   0.169  1.00 35.16      C1
ATOM  2951 CE1 TYR  440      62.625  43.037   1.532  1.00 36.66      C1
ATOM  2952 CD2 TYR  440      65.126  43.064   0.385  1.00 37.81      C1
ATOM  2953 CE2 TYR  440      64.992  42.881   1.752  1.00 39.02      C1
ATOM  2954 CZ  TYR  440      63.741  42.864   2.317  1.00 37.34      C1
ATOM  2955 OH  TYR  440      63.637  42.649   3.678  1.00 37.56      C1
ATOM  2956 HH  TYR  440      64.498  42.343   3.988  1.00 0.00       C1
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FIGURE 5

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FIGURE 5

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ATOM  3059 CD1 LEU  451     58.833   ...284  -8.653  1.00 59.12      C1
ATOM  3060 CD2 LEU  451     58.369  34.511  -7.751  1.00 58.27      C1
ATOM  3061 C   LEU  451     54.785  32.700  -9.280  1.00 55.96      C1
ATOM  3062 O   LEU  451     54.717  31.935  -8.319  1.00 53.74      C1
ATOM  3063 N   GLY  452     53.774  33.533  -9.522  1.00 57.52      C1
ATOM  3064 H   GLY  452     53.889  34.241 -10.191  1.00  0.00      C1
ATOM  3065 CA  GLY  452     52.567  33.515  -8.710  1.00 60.66      C1
ATOM  3066 C   GLY  452     51.942  32.137  -8.772  1.00 63.64      C1
ATOM  3067 O   GLY  452     51.476  31.593  -7.782  1.00 62.60      C1
ATOM  3068 N   HIS  453     52.089  31.545  -9.969  1.00 68.46      C1
ATOM  3069 H   HIS  453     52.628  32.040 -10.618  1.00  0.00      C1
ATOM  3070 CA  HIS  453     51.606  30.205 -10.326  1.00 72.27      C1
ATOM  3071 CB  HIS  453     51.785  29.908 -11.828  1.00 73.84      C1
ATOM  3072 CG  HIS  453     51.421  31.061 -12.777  1.00 77.81      C1
ATOM  3073 CD2 HIS  453     50.599  32.148 -12.498  1.00 79.29      C1
ATOM  3074 ND1 HIS  453     51.886  31.244 -14.012  1.00 79.84      C1
ATOM  3075 HD1 HIS  453     52.617  30.739 -14.475  1.00  0.00      C1
ATOM  3076 CE1 HIS  453     51.385  32.382 -14.470  1.00 81.11      C1
ATOM  3077 NE2 HIS  453     50.613  32.923 -13.551  1.00 79.85      C1
ATOM  3078 HE2 HIS  453     50.230  33.825 -13.586  1.00  0.00      C1
ATOM  3079 C   HIS  453     52.454  29.235  -9.515  1.00 73.43      C1
ATOM  3080 O   HIS  453     51.875  28.531  -8.692  1.00 73.56      C1
ATOM  3081 N   SER  454     53.785  29.207  -9.651  1.00 74.64      C1
ATOM  3082 H   SER  454     54.214  29.730 -10.351  1.00  0.00      C1
ATOM  3083 CA  SER  454     52.639  28.411  -8.765  1.00 77.07      C1
ATOM  3084 CB  SER  454     56.123  28.762  -8.980  1.00 77.34      C1
ATOM  3085 OG  SER  454     57.095  27.715  -9.124  1.00 75.28      C1
ATOM  3086 HG  SER  454     57.149  27.211  -8.306  1.00  0.00      C1
ATOM  3087 C   SER  454     54.332  28.608  -7.262  1.00 78.84      C1
ATOM  3088 O   SER  454     54.270  27.617  -6.535  1.00 80.57      C1
ATOM  3089 N   LEU  455     54.070  29.789  -6.693  1.00 79.72      C1
ATOM  3090 H   LEU  455     53.956  30.582  -7.250  1.00  0.00      C1
ATOM  3091 CA  LEU  455     53.849  29.915  -5.257  1.00 80.43      C1
ATOM  3092 CB  LEU  455     54.085  31.347  -4.838  1.00 80.20      C1
ATOM  3093 CG  LEU  455     55.389  31.981  -5.269  1.00 81.67      C1
ATOM  3094 CD1 LEU  455     55.254  33.494  -5.419  1.00 81.36      C1
ATOM  3095 CD2 LEU  455     56.431  31.579  -4.264  1.00 82.26      C1
ATOM  3096 C   LEU  455     52.438  29.510  -4.848  1.00 81.56      C1
ATOM  3097 O   LEU  455     52.038  29.893  -3.741  1.00 82.22      C1
ATOM  3098 N   GLY  456     51.653  28.816  -5.708  1.00 81.89      C1
ATOM  3099 H   GLY  456     52.036  28.592  -6.584  1.00  0.00      C1
ATOM  3100 CA  GLY  456     50.269  28.361  -5.467  1.00 82.22      C1
ATOM  3101 C   GLY  456     49.220  29.386  -4.973  1.00 82.56      C1
ATOM  3102 O   GLY  456     48.268  28.989  -4.276  1.00 82.38      C1
ATOM  3103 N   ILE  457     49.347  30.697  -5.286  1.00 82.54      C1
ATOM  3104 H   ILE  457     50.075  30.942  -5.894  1.00  0.00      C1
ATOM  3105 CA  ILE  457     48.435  31.761  -4.824  1.00 81.63      C1
ATOM  3106 CB  ILE  457     49.110  33.157  -5.086  1.00 80.69      C1
ATOM  3107 CG2 ILE  457     48.218  34.305  -4.662  1.00 79.76      C1
ATOM  3108 CG1 ILE  457     50.369  33.275  -4.253  1.00 79.82      C1
ATOM  3109 CD ILE  457     51.506  33.868  -5.081  1.00 77.89      C1
ATOM  3110 C   ILE  457     47.048  31.698  -5.472  1.00 81.70      C1
ATOM  3111 O   ILE  457     46.903  31.761  -6.700  1.00 82.57      C1
ATOM  3112 N   PRO  458     45.963  31.583  -4.705  1.00 81.40      C1
ATOM  3113 CD  PRO  458     45.959  31.225  -3.278  1.00 81.21      C1
ATOM  3114 CA  PRO  458     44.607  31.643  -5.264  1.00 80.57      C1
ATOM  3115 CB  PRO  458     43.779  30.942  -4.157  1.00 81.12      C1
ATOM  3116 CG  PRO  458     44.757  30.293  -3.171  1.00 80.47      C1
ATOM  3117 C   PRO  458     44.120  33.063  -5.648  1.00 79.70      C1
ATOM  3118 O   PRO  458     43.674  33.736  -4.718  1.00 80.10      C1
ATOM  3119 N   TRP  459     44.171  33.662  -6.861  1.00 78.09      C1
ATOM  3120 H   TRP  459     44.614  33.105  -7.591  1.00  0.00      C1
ATOM  3121 CA  TRP  459     43.543  34.986  -7.092  1.00 77.73      C1
ATOM  3122 CB  TRP  459     43.802  35.428  -8.522  1.00 78.71      C1
ATOM  3123 CG  TRP  459     43.054  36.677  -9.017  1.00 81.57      C1
ATOM  3124 CD2 TRP  459     41.802  36.771  -9.618  1.00 82.89      C1
ATOM  3125 CE2 TRP  459     41.717  38.139  -9.883  1.00 84.21      C1
ATOM  3126 CE3 TRP  459     40.738  35.960  -9.983  1.00 84.28      C1
ATOM  3127 CD1 TRP  459     43.661  37.899  -8.925  1.00 83.89      C1
ATOM  3128 NE1 TRP  459     42.828  38.765  -9.460  1.00 85.23      C1
ATOM  3129 HE1 TRP  459     42.944  39.738  -9.483  1.00  0.00      C1
ATOM  3130 CZ2 TRP  459     40.615  38.727 -10.494  1.00 84.17      C1
ATOM  3131 CZ3 TRP  459     39.637  36.538 -10.597  1.00 84.56      C1
ATOM  3132 CH2 TRP  459     39.562  37.904 -10.852  1.00 84.83      C1
ATOM  3133 C   TRP  459     42.009  35.013  -6.837  1.00 77.31      C1
ATOM  3134 O   TRP  459     41.202  34.744  -7.726  1.00 76.88      C1
ATOM  3135 N   ALA  460     41.657  35.969  -6.020  1.00 76.81      C1
ATOM  3136 H   ALA  460     42.187  36.640  -5.589  1.00  0.00      C1
ATOM  3137 CA  ALA  460     40.158  36.044  -5.613  1.00 76.44      C1
ATOM  3138 CB  ALA  460     40.072  36.724  -4.248  1.00 75.51      C1
ATOM  3139 C   ALA  460     39.617  36.538  -6.729  1.00 76.29      C1
ATOM  3140 O   ALA  460     39.449  37.976  -6.833  1.00 76.98      C1
ATOM  3141 N   PRO  461     38.217  36.147  -7.187  1.00 76.66      C1
ATOM  3142 CD  PRO  461     38.104  34.684  -7.245  1.00 75.88      C1
ATOM  3143 CA  PRO  461     37.242  36.793  -8.068  1.00 75.46      C1
ATOM  3144 CB  PRO  461     36.605  35.605  -8.755  1.00 75.71      C1
ATOM  3145 CG  PRO  461     36.703  34.458  -7.767  1.00 75.60      C1
ATOM  3146 C   PRO  461     36.271  37.803  -7.545  1.00 75.71      C1
ATOM  3147 O   PRO  461     35.677  37.734  -6.440  1.00 73.66      C1
ATOM  3148 N   LEU  462     35.996  38.767  -8.449  1.00 77.19      C1
ATOM  3149 H   LEU  462     36.516  38.723  -9.277  1.00  0.00      C1
ATOM  3150 CA  LEU  462     35.069  39.891  -8.275  1.00 78.32      C1
ATOM  3151 CB  LEU  462     35.674  40.984  -7.360  1.00 78.09      C1
ATOM  3152 CG  LEU  462     34.786  41.959  -6.558  1.00 78.09      C1
ATOM  3153 CD1 LEU  462     34.051  42.987  -7.406  1.00 78.52      C1
ATOM  3154 CD2 LEU  462     33.767  41.092  -5.828  1.00 78.62      C1
ATOM  3155 C   LEU  462     34.701  40.565  -9.611  1.00 80.64      C1
ATOM  3156 OT1 LEU  462     33.507  40.842  -9.808  1.00 81.74      C1
ATOM  3157 OT2 LEU  462     35.606  40.847 -10.417  1.00 81.39      C2
ATOM  3158 CB  LEU  472     22.074  42.654  -1.426  1.00 64.74      C2
ATOM  3159 CG  LEU  472     22.278  44.145  -1.189  1.00 59.58      C2
ATOM  3160 CD1 LEU  472     23.496  44.325  -0.328  1.00 59.14      C2
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FIGURE 5

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ATOM  3161 CD2 LEU  472     22.501  -4.883  -2.486  1.00 56.85      C2
ATOM  3162 C   LEU  472     23.504  40.625  -1.996  1.00 63.91      C2
ATOM  3163 O   LEU  472     23.738  39.874  -2.949  1.00 64.90      C2
ATOM  3164 1HT1 LEU  472    21.563  41.441  -3.595  1.00  0.00      C2
ATOM  3165 1HT2 LEU  472    23.091  41.291  -4.237  1.00  0.00      C2
ATOM  3166 N   LEU  472     22.472  41.930  -3.693  1.00 64.29      C2
ATOM  3167 1HT3 LEU  472    22.358  42.849  -4.160  1.00  0.00      C2
ATOM  3168 CA  LEU  472     23.092  42.037  -2.386  1.00 63.85      C2
ATOM  3169 N   ALA  473     23.652  40.229  -0.733  1.00 63.02      C2
ATOM  3170 1H  ALA  473     23.533  40.867   0.002  1.00  0.00      C2
ATOM  3171 CA  ALA  473     24.023  38.861  -0.353  1.00 62.37      C2
ATOM  3172 CB  ALA  473     22.870  37.939  -0.558  1.00 63.65      C2
ATOM  3173 C   ALA  473     25.196  38.354  -1.126  1.00 62.01      C2
ATOM  3174 O   ALA  473     26.301  38.651  -0.715  1.00 63.36      C2
ATOM  3175 N   GLY  474     25.032  37.784  -2.306  1.00 61.43      C2
ATOM  3176 H   GLY  474     24.148  37.818  -2.722  1.00  0.00      C2
ATOM  3177 CA  GLY  474     26.101  37.137  -3.047  1.00 63.80      C2
ATOM  3178 C   GLY  474     27.354  37.950  -3.356  1.00 65.13      C2
ATOM  3179 O   GLY  474     28.482  37.417  -3.257  1.00 66.24      C2
ATOM  3180 N   CYS  475     27.175  39.237  -3.757  1.00 64.88      C2
ATOM  3181 H   CYS  475     26.261  39.550  -3.885  1.00  0.00      C2
ATOM  3182 CA  CYS  475     28.308  40.127  -4.068  1.00 61.84      C2
ATOM  3183 CB  CYS  475     27.925  41.413  -4.806  1.00 63.74      C2
ATOM  3184 SG  CYS  475     29.494  42.075  -5.437  1.00 68.86      C2
ATOM  3185 C   CYS  475     28.995  40.567  -2.795  1.00 57.30      C2
ATOM  3186 O   CYS  475     30.214  40.449  -2.724  1.00 57.14      C2
ATOM  3187 N   LEU  476     28.230  40.983  -1.779  1.00 53.29      C2
ATOM  3188 H   LEU  476     27.264  41.024  -1.885  1.00  0.00      C2
ATOM  3189 CA  LEU  476     28.797  41.315  -0.493  1.00 50.43      C2
ATOM  3190 CB  LEU  476     27.719  41.723   0.523  1.00 45.68      C2
ATOM  3191 CG  LEU  476     27.130  43.165   0.497  1.00 42.80      C2
ATOM  3192 CD1 LEU  476     26.670  43.559   1.896  1.00 36.25      C2
ATOM  3193 CD2 LEU  476     28.180  44.180   0.057  1.00 40.22      C2
ATOM  3194 C   LEU  476     29.546  40.108   0.042  1.00 50.42      C2
ATOM  3195 O   LEU  476     30.614  40.222   0.646  1.00 50.61      C2
ATOM  3196 N   SER  477     29.053  38.922  -0.270  1.00 50.62      C2
ATOM  3197 H   SER  477     28.196  38.860  -0.729  1.00  0.00      C2
ATOM  3198 CA  SER  477     29.721  37.712   0.125  1.00 51.41      C2
ATOM  3199 CB  SER  477     28.778  36.524  -0.051  1.00 49.63      C2
ATOM  3200 OG  SER  477     27.732  36.616   0.926  1.00 57.65      C2
ATOM  3201 HG  SER  477     27.280  37.462   0.828  1.00  0.00      C2
ATOM  3202 C   SER  477     30.978  37.525  -0.681  1.00 50.75      C2
ATOM  3203 O   SER  477     31.980  37.143  -0.068  1.00 51.41      C2
ATOM  3204 N   GLN  478     31.037  37.788  -1.984  1.00 50.21      C2
ATOM  3205 H   GLN  478     30.222  38.056  -2.457  1.00  0.00      C2
ATOM  3206 CA  GLN  478     32.307  37.697  -2.715  1.00 51.37      C2
ATOM  3207 CB  GLN  478     32.064  37.929  -4.166  1.00 53.65      C2
ATOM  3208 CG  GLN  478     31.983  36.570  -4.788  1.00 57.32      C2
ATOM  3209 CD  GLN  478     31.354  36.649  -6.160  1.00 60.47      C2
ATOM  3210 OE1 GLN  478     31.999  36.504  -7.205  1.00 62.26      C2
ATOM  3211 NE2 GLN  478     30.045  36.878  -6.167  1.00 62.16      C2

ATOM  3212 HE21 GLN  478    29.569  36.972  -5.317  1.00  0.00      C2
ATOM  3213 HE22 GLN  478    29.641  36.928  -7.054  1.00  0.00      C2
ATOM  3214 C   GLN  478     33.398  38.670  -2.249  1.00 50.66      C2
ATOM  3215 O   GLN  478     34.584  38.314  -2.217  1.00 50.13      C2
ATOM  3216 N   LEU  479     33.045  39.909  -1.859  1.00 48.78      C2
ATOM  3217 H   LEU  479     32.131  40.223  -2.039  1.00  0.00      C2
ATOM  3218 CA  LEU  479     34.015  40.800  -1.245  1.00 45.87      C2
ATOM  3219 CB  LEU  479     33.434  42.141  -0.827  1.00 47.05      C2
ATOM  3220 CG  LEU  479     32.853  43.083  -1.818  1.00 49.40      C2
ATOM  3221 CD1 LEU  479     32.596  44.391  -1.078  1.00 48.15      C2
ATOM  3222 CD2 LEU  479     33.779  43.258  -3.000  1.00 48.59      C2
ATOM  3223 C   LEU  479     34.505  40.146   0.056  1.00 42.33      C2
ATOM  3224 O   LEU  479     35.695  39.955   0.262  1.00 40.90      C2
ATOM  3225 N   HIS  480     33.609  39.766   0.950  1.00 39.56      C2
ATOM  3226 H   HIS  480     32.658  39.935   0.763  1.00  0.00      C2
ATOM  3227 CA  HIS  480     33.979  39.108   2.179  1.00 37.81      C2
ATOM  3228 CB  HIS  480     32.742  38.714   2.972  1.00 34.29      C2
ATOM  3229 CG  HIS  480     33.094  38.341   4.369  1.00 33.82      C2
ATOM  3230 CD2 HIS  480     33.121  36.932   4.709  1.00 32.44      C2
ATOM  3231 ND1 HIS  480     33.450  38.995   5.344  1.00 34.27      C2
ATOM  3232 HD1 HIS  480     33.505  39.976   5.362  1.00  0.00      C2
ATOM  3233 CE1 HIS  480     33.706  38.223   6.365  1.00 33.80      C2
ATOM  3234 NE2 HIS  480     33.504  36.986   5.965  1.00 32.12      C2
ATOM  3235 HE2 HIS  480     33.637  36.202   6.544  1.00  0.00      C2
ATOM  3236 C   HIS  480     34.836  37.860   1.961  1.00 39.08      C2
ATOM  3237 O   HIS  480     35.716  37.631   2.791  1.00 40.93      C2
ATOM  3238 N   SER  481     34.615  37.029   0.935  1.00 38.24      C2
ATOM  3239 H   SER  481     33.900  37.241   0.305  1.00  0.00      C2
ATOM  3240 CA  SER  481     35.391  35.818   0.683  1.00 38.17      C2
ATOM  3241 CB  SER  481     34.813  34.943  -0.420  1.00 40.42      C2
ATOM  3242 OG  SER  481     33.454  34.597  -0.137  1.00 47.63      C2
ATOM  3243 HG  SER  481     32.898  35.385  -0.162  1.00  0.00      C2
ATOM  3244 C   SER  481     36.724  36.272   0.211  1.00 36.12      C2
ATOM  3245 O   SER  481     37.692  35.793   0.765  1.00 36.23      C2
ATOM  3246 N   GLY  482     36.786  37.206  -0.744  1.00 36.21      C2
ATOM  3247 H   GLY  482     35.956  37.498  -1.168  1.00  0.00      C2
ATOM  3248 CA  GLY  482     38.028  37.792  -1.206  1.00 36.50      C2
ATOM  3249 C   GLY  482     38.958  38.296  -0.151  1.00 36.14      C2
ATOM  3250 O   GLY  482     40.142  37.936  -0.055  1.00 36.65      C2
ATOM  3251 N   LEU  483     38.381  39.084   0.750  1.00 34.04      C2
ATOM  3252 H   LEU  483     37.445  39.326   0.608  1.00  0.00      C2
ATOM  3253 CA  LEU  483     39.073  39.593   1.900  1.00 32.07      C2
ATOM  3254 CB  LEU  483     38.134  40.442   2.731  1.00 31.17      C2
ATOM  3255 CG  LEU  483     37.535  41.687   2.081  1.00 31.11      C2
ATOM  3256 CD1 LEU  483     36.757  42.411   3.156  1.00 30.82      C2
ATOM  3257 CD2 LEU  483     38.599  42.593   1.480  1.00 29.56      C2
ATOM  3258 C   LEU  483     39.600  38.461   2.745  1.00 32.91      C2
ATOM  3259 O   LEU  483     40.752  38.498   3.199  1.00 31.25      C2
ATOM  3260 N   PHE  484     38.767  37.422   2.925  1.00 34.08      C2
ATOM  3261 H   PHE  484     37.920  37.608   2.471  1.00  0.00      C2
ATOM  3262 CA  PHE  484     39.105  36.298   3.788  1.00 34.60      C2
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FIGURE 5

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ATOM  3263 CB  PHE  484      37.975  35.300   3.925  1.00 37.46      C2
ATOM  3264 CG  PHE  484      38.268  34.183   4.897  1.00 40.86      C2
ATOM  3265 CD1 PHE  484      38.219  32.884   4.482  1.00 45.62      C2
ATOM  3266 CD2 PHE  484      38.528  34.445   6.210  1.00 43.62      C2
ATOM  3267 CE1 PHE  484      38.421  31.858   5.395  1.00 47.98      C2
ATOM  3268 CE2 PHE  484      38.731  33.427   7.119  1.00 46.78      C2
ATOM  3269 CZ  PHE  484      38.677  32.119   6.720  1.00 48.06      C2
ATOM  3270 C   PHE  484      40.245  35.602   3.113  1.00 33.92      C2
ATOM  3271 O   PHE  484      41.162  35.289   3.826  1.00 34.25      C2
ATOM  3272 N   LEU  485      40.326  35.413   1.799  1.00 32.75      C2
ATOM  3273 H   LEU  485      39.577  35.717   1.250  1.00  0.00      CZ
ATOM  3274 CA  LEU  485      41.475  34.778   1.163  1.00 33.74      C2
ATOM  3275 CB  LEU  485      41.183  34.629  -0.305  1.00 35.35      C2
ATOM  3276 CG  LEU  485      42.101  33.962  -1.275  1.00 37.80      C2
ATOM  3277 CD1 LEU  485      41.181  33.404  -2.345  1.00 41.44      C2
ATOM  3278 CD2 LEU  485      43.125  34.903  -1.899  1.00 40.07      C2
ATOM  3279 C   LEU  485      42.740  35.585   1.376  1.00 33.95      C2
ATOM  3280 O   LEU  485      43.766  35.060   1.850  1.00 33.84      C2
ATOM  3281 N   TYR  486      42.609  36.885   1.034  1.00 33.67      C2
ATOM  3282 H   TYR  486      41.757  37.186   0.659  1.00  0.00      CZ
ATOM  3283 CA  TYR  486      43.662  37.862   1.242  1.00 31.33      C2
ATOM  3284 CB  TYR  486      43.210  39.290   0.714  1.00 35.33      C2
ATOM  3285 CG  TYR  486      43.300  39.325  -0.825  1.00 33.17      C2
ATOM  3286 CD1 TYR  486      42.154  39.405  -1.579  1.00 32.79      C2
ATOM  3287 CE1 TYR  486      42.228  39.290  -2.944  1.00 33.73      C2
ATOM  3288 CD2 TYR  486      44.533  39.153  -1.445  1.00 34.59      C2
ATOM  3289 CE2 TYR  486      44.618  39.033  -2.818  1.00 34.63      C2
ATOM  3290 CZ  TYR  486      43.451  39.096  -3.562  1.00 35.58      C2
ATOM  3291 OH  TYR  486      43.484  38.880  -4.942  1.00 38.24      C2
ATOM  3292 HH  TYR  486      42.614  39.086  -5.306  1.00  0.00      C2
ATOM  3293 C   TYR  486      44.068  37.905   2.697  1.00 27.39      C2
ATOM  3294 O   TYR  486      45.258  38.007   2.942  1.00 30.19      C2
ATOM  3295 N   GLN  487      43.270  37.691   3.708  1.00 26.95      C2
ATOM  3296 H   GLN  487      42.315  37.545   3.565  1.00  0.00      C2
ATOM  3297 CA  GLN  487      43.835  37.646   5.031  1.00 28.33      C2
ATOM  3298 CB  GLN  487      42.690  37.578   6.050  1.00 32.66      C2
ATOM  3299 CG  GLN  487      43.092  37.979   7.485  1.00 37.50      C2
ATOM  3300 CD  GLN  487      43.966  39.252   7.469  1.00 40.54      C2
ATOM  3301 OE1 GLN  487      43.441  40.346   7.292  1.00 40.45      C2
ATOM  3302 NE2 GLN  487      45.305  39.206   7.549  1.00 38.19      C2
ATOM  3303 HE21 GLN  487      45.755  40.057   7.452  1.00  0.00      C2
ATOM  3304 HE22 GLN  487      45.736  38.340   7.702  1.00  0.00      C2
ATOM  3305 C   GLN  487      44.791  36.455   5.207  1.00 28.53      C2
ATOM  3306 O   GLN  487      45.774  36.542   5.964  1.00 28.72      C2
ATOM  3307 N   GLY  488      44.550  35.363   4.454  1.00 28.32      C2
ATOM  3308 H   GLY  488      43.799  35.400   3.824  1.00  0.00      C2
ATOM  3309 CA  GLY  488      45.291  34.120   4.557  1.00 26.04      C2
ATOM  3310 C   GLY  488      46.660  34.264   4.033  1.00 25.75      C2
ATOM  3311 O   GLY  488      47.660  33.946   4.712  1.00 25.86      C2
ATOM  3312 N   LEU  489      46.655  34.798   2.818  1.00 25.05      C2
ATOM  3313 H   LEU  489      45.798  35.062   2.416  1.00  0.00      C2
ATOM  3314 CA  LEU  489      47.911  34.990   2.099  1.00 25.63      C2
ATOM  3315 CB  LEU  489      47.708  35.570   0.725  1.00 27.66      C2
ATOM  3316 CG  LEU  489      46.761  34.755  -0.189  1.00 30.83      C2
ATOM  3317 CD1 LEU  489      46.373  35.506  -1.471  1.00 30.43      C2
ATOM  3318 CD2 LEU  489      47.472  33.454  -0.502  1.00 32.62      C2
ATOM  3319 C   LEU  489      48.783  35.936   2.853  1.00 25.28      C2
ATOM  3320 O   LEU  489      49.973  35.705   2.914  1.00 27.37      C2
ATOM  3321 N   LEU  490      48.237  36.935   3.534  1.00 25.79      C2
ATOM  3322 H   LEU  490      47.267  37.079   3.515  1.00  0.00      CZ
ATOM  3323 CA  LEU  490      49.072  37.868   4.220  1.00 25.96      C2
ATOM  3324 CB  LEU  490      48.274  39.139   4.567  1.00 27.96      C2
ATOM  3325 CG  LEU  490      47.823  40.131   3.474  1.00 27.89      C2
ATOM  3326 CD1 LEU  490      46.772  41.019   4.123  1.00 28.03      C2
ATOM  3327 CD2 LEU  490      48.988  40.942   2.899  1.00 28.15      C2
ATOM  3328 C   LEU  490      49.619  37.243   5.459  1.00 27.33      C2
ATOM  3329 O   LEU  490      50.740  37.528   5.865  1.00 26.73      C2
ATOM  3330 N   GLN  491      48.883  36.370   6.111  1.00 29.88      C2
ATOM  3331 H   GLN  491      47.984  36.127   5.799  1.00  0.00      CZ
ATOM  3332 CA  GLN  491      49.430  35.809   7.314  1.00 33.03      C2
ATOM  3333 CB  GLN  491      48.305  35.113   8.027  1.00 38.68      C2
ATOM  3334 CG  GLN  491      47.856  35.963   9.197  1.00 46.07      C2
ATOM  3335 CD  GLN  491      46.548  36.262   9.278  1.00 50.83      C2
ATOM  3336 OE1 GLN  491      45.965  37.436   9.402  1.00 51.92      C2
ATOM  3337 NE2 GLN  491      45.425  35.294   9.278  1.00 51.67      C2
ATOM  3338 HE21 GLN  491      45.723  34.353   9.288  1.00  0.00      C2
ATOM  3339 HE22 GLN  491      44.489  35.560   9.288  1.00  0.00      C2
ATOM  3340 C   GLN  491      50.582  34.867   6.986  1.00 33.58      C2
ATOM  3341 O   GLN  491      51.582  34.828   7.715  1.00 34.65      C2
ATOM  3342 N   ALA  492      50.482  34.191   5.824  1.00 34.15      C2
ATOM  3343 H   ALA  492      49.703  34.382   5.264  1.00  0.00      C2
ATOM  3344 CA  ALA  492      51.416  33.177   5.321  1.00 33.64      C2
ATOM  3345 CB  ALA  492      50.818  32.500   4.081  1.00 33.67      C2
ATOM  3346 C   ALA  492      52.802  33.678   4.959  1.00 34.79      C2
ATOM  3347 O   ALA  492      53.789  32.943   4.879  1.00 34.03      C2
ATOM  3348 N   LEU  493      52.885  34.981   4.728  1.00 35.94      C2
ATOM  3349 H   LEU  493      52.060  35.510   4.721  1.00  0.00      CZ
ATOM  3350 CA  LEU  493      54.139  35.634   4.426  1.00 34.86      C2
ATOM  3351 CB  LEU  493      53.898  36.990   3.747  1.00 31.36      C2
ATOM  3352 CG  LEU  493      53.127  37.065   2.443  1.00 28.47      C2
ATOM  3353 CD1 LEU  493      52.715  38.495   2.214  1.00 31.74      C2
ATOM  3354 CD2 LEU  493      53.977  36.608   1.285  1.00 28.79      C2
ATOM  3355 C   LEU  493      54.879  35.843   5.721  1.00 36.15      C2
ATOM  3356 O   LEU  493      55.985  36.374   5.694  1.00 36.70      C2
ATOM  3357 N   GLU  494      54.300  35.497   6.855  1.00 38.35      C2
ATOM  3358 H   GLU  494      53.395  35.130   6.836  1.00  0.00      CZ
ATOM  3359 CA  GLU  494      54.910  35.648   8.157  1.00 43.14      C2
ATOM  3360 CB  GLU  494      55.621  34.340   8.545  1.00 46.61      C2
ATOM  3361 CG  GLU  494      54.711  33.471   9.419  1.00 53.71      C2
ATOM  3362 CD  GLU  494      54.195  32.160   8.785  1.00 60.27      C2
ATOM  3363 OE1 GLU  494      53.146  31.653   9.230  1.00 63.52      C2
ATOM  3364 OE2 GLU  494      54.839  31.630   7.862  1.00 62.76      C2
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FIGURE 5

FIGURE 5

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ATOM  3467 CG  LEU  507     48.010  44.919   3.858  1.00 20.85      C2
ATOM  3468 CD1 LEU  507     46.771  45.650   3.455  1.00 24.13      C2
ATOM  3469 CD2 LEU  507     49.074  45.055   2.842  1.00 20.13      C2
ATOM  3470 C   LEU  507     46.766  44.640   6.880  1.00 24.09      C2
ATOM  3471 O   LEU  507     45.600  44.764   6.541  1.00 25.80      C2
ATOM  3472 N   GLN  508     47.152  43.618   7.661  1.00 24.01      C2
ATOM  3473 H   GLN  508     48.112  43.555   7.866  1.00  0.00      C2
ATOM  3474 CA  GLN  508     46.228  42.625   8.214  1.00 23.71      C2
ATOM  3475 CB  GLN  508     46.961  41.627   9.036  1.00 23.83      C2
ATOM  3476 CG  GLN  508     47.937  40.899   8.173  1.00 31.64      C2
ATOM  3477 CD  GLN  508     48.842  40.080   9.054  1.00 34.00      C2
ATOM  3478 OE1 GLN  508     50.031  40.346   9.161  1.00 38.32      C2
ATOM  3479 NE2 GLN  508     48.321  39.090   9.748  1.00 36.30      C2
ATOM  3480 HE21 GLN  508     47.373  38.880   9.639  1.00  0.00      C2
ATOM  3481 HE22 GLN  508     48.891  38.636  10.406  1.00  0.00      C2
ATOM  3482 C   GLN  508     45.105  43.123   9.111  1.00 24.24      C2
ATOM  3483 O   GLN  508     43.978  42.650   9.014  1.00 24.06      C2
ATOM  3484 N   LEU  509     45.375  44.019  10.090  1.00 26.07      C2
ATOM  3485 H   LEU  509     46.316  44.262  10.272  1.00  0.00      C2
ATOM  3486 CA  LEU  509     44.378  44.640  10.977  1.00 25.71      C2
ATOM  3487 CB  LEU  509     44.993  45.555  12.031  1.00 25.60      C2
ATOM  3488 CG  LEU  509     45.838  44.757  13.042  1.00 29.00      C2
ATOM  3489 CD1 LEU  509     46.658  45.705  13.886  1.00 28.93      C2
ATOM  3490 CD2 LEU  509     44.950  43.919  13.937  1.00 27.94      C2
ATOM  3491 C   LEU  509     43.465  45.471  10.130  1.00 25.17      C2
ATOM  3492 O   LEU  509     42.274  45.411  10.408  1.00 27.22      C2
ATOM  3493 N   ASP  510     43.899  46.208   9.101  1.00 23.77      C2
ATOM  3494 H   ASP  510     44.865  46.277   8.930  1.00  0.00      C2
ATOM  3495 CA  ASP  510     42.955  46.898   8.240  1.00 22.60      C2
ATOM  3496 CB  ASP  510     43.652  47.829   7.306  1.00 25.21      C2
ATOM  3497 CG  ASP  510     44.316  48.966   8.068  1.00 33.01      C2
ATOM  3498 OD1 ASP  510     45.178  49.621   7.477  1.00 34.28      C2
ATOM  3499 OD2 ASP  510     43.988  49.209   9.250  1.00 34.44      C2
ATOM  3500 C   ASP  510     42.104  45.980   7.398  1.00 23.72      C2
ATOM  3501 O   ASP  510     40.897  46.220   7.387  1.00 24.80      C2
ATOM  3502 N   VAL  511     42.632  44.984   6.659  1.00 22.38      C2
ATOM  3503 H   VAL  511     43.611  44.900   6.620  1.00  0.00      C2
ATOM  3504 CA  VAL  511     41.823  44.010   5.961  1.00 21.89      C2
ATOM  3505 CB  VAL  511     42.752  42.924   5.366  1.00 22.71      C2
ATOM  3506 CG1 VAL  511     41.954  41.756   4.792  1.00 20.43      C2
ATOM  3507 CG2 VAL  511     43.529  43.524   4.210  1.00 16.19      C2
ATOM  3508 C   VAL  511     40.827  43.403   6.960  1.00 21.92      C2
ATOM  3509 O   VAL  511     39.625  43.447   6.719  1.00 23.46      C2
ATOM  3510 N   ALA  512     41.258  43.017   8.163  1.00 20.49      C2
ATOM  3511 H   ALA  512     42.216  43.063   8.361  1.00  0.00      C2
ATOM  3512 CA  ALA  512     40.388  42.357   9.108  1.00 20.83      C2
ATOM  3513 CB  ALA  512     41.103  41.974  10.344  1.00 17.89      C2
ATOM  3514 C   ALA  512     39.250  43.205   9.550  1.00 23.89      C2
ATOM  3515 O   ALA  512     38.201  42.668   9.874  1.00 24.61      C2
ATOM  3516 N   ASP  513     39.417  44.539   9.544  1.00 25.96      C2
ATOM  3517 H   ASP  513     40.300  44.888   9.291  1.00  0.00      C2
ATOM  3518 CA  ASP  513     38.374  45.471   9.947  1.00 25.37      C2
ATOM  3519 CB  ASP  513     38.958  46.787  10.373  1.00 26.88      C2
ATOM  3520 CG  ASP  513     39.682  46.679  11.712  1.00 32.35      C2
ATOM  3521 OD1 ASP  513     40.371  47.644  12.058  1.00 25.06      C2
ATOM  3522 OD2 ASP  513     39.580  45.646  12.390  1.00 34.10      C2
ATOM  3523 C   ASP  513     37.392  45.730   8.846  1.00 24.95      C2
ATOM  3524 O   ASP  513     36.185  45.868   9.090  1.00 26.92      C2
ATOM  3525 N   PHE  514     37.867  45.739   7.634  1.00 22.88      C2
ATOM  3526 H   PHE  514     38.829  45.614   7.475  1.00  0.00      C2
ATOM  3527 CA  PHE  514     36.974  45.922   6.530  1.00 24.09      C2
ATOM  3528 CB  PHE  514     37.812  46.061   5.266  1.00 18.11      C2
ATOM  3529 CG  PHE  514     36.956  46.470   4.072  1.00 17.86      C2
ATOM  3530 CD1 PHE  514     35.715  47.089   4.245  1.00 15.18      C2
ATOM  3531 CD2 PHE  514     37.440  46.197   2.804  1.00 13.77      C2
ATOM  3532 CE1 PHE  514     34.983  47.419   3.130  1.00 14.51      C2
ATOM  3533 CE2 PHE  514     36.693  46.539   1.705  1.00 12.10      C2
ATOM  3534 CZ  PHE  514     35.468  47.146   1.868  1.00 10.68      C2
ATOM  3535 C   PHE  514     36.026  44.703   6.450  1.00 29.23      C2
ATOM  3536 O   PHE  514     34.788  44.828   6.350  1.00 29.80      C2
ATOM  3537 N   ALA  515     36.604  43.490   6.531  1.00 31.15      C2
ATOM  3538 H   ALA  515     37.581  43.450   6.639  1.00  0.00      C2
ATOM  3539 CA  ALA  515     35.839  42.260   6.416  1.00 32.36      C2
ATOM  3540 CB  ALA  515     36.851  41.126   6.402  1.00 37.35      C2
ATOM  3541 C   ALA  515     34.801  42.089   7.515  1.00 32.39      C2
ATOM  3542 O   ALA  515     33.676  41.609   7.331  1.00 32.63      C2
ATOM  3543 N   THR  516     35.164  42.457   8.735  1.00 33.01      C2
ATOM  3544 H   THR  516     36.117  42.578   8.935  1.00  0.00      C2
ATOM  3545 CA  THR  516     34.231  42.566   9.821  1.00 35.18      C2
ATOM  3546 CB  THR  516     35.016  43.018  10.988  1.00 35.40      C2
ATOM  3547 OG1 THR  516     35.685  41.818  11.336  1.00 42.65      C2
ATOM  3548 HG1 THR  516     36.505  41.713  10.816  1.00  0.00      C2
ATOM  3549 CG2 THR  516     34.262  43.672  12.097  1.00 35.56      C2
ATOM  3550 C   THR  516     33.140  43.554   9.482  1.00 37.62      C2
ATOM  3551 O   THR  516     32.005  43.315   9.857  1.00 40.37      C2
ATOM  3552 N   THR  517     33.387  44.666   8.802  1.00 38.61      C2
ATOM  3553 H   THR  517     34.291  44.850   8.469  1.00  0.00      C2
ATOM  3554 CA  THR  517     32.359  45.641   8.512  1.00 38.92      C2
ATOM  3555 CB  THR  517     33.123  46.903   7.962  1.00 40.46      C2
ATOM  3556 OG1 THR  517     33.832  47.429   9.103  1.00 43.22      C2
ATOM  3557 HG1 THR  517     34.536  46.815   9.335  1.00  0.00      C2
ATOM  3558 CG2 THR  517     32.232  47.926   7.253  1.00 39.90      C2
ATOM  3559 C   THR  517     31.343  45.012   7.551  1.00 38.30      C2
ATOM  3560 O   THR  517     30.137  45.125   7.811  1.00 38.69      C2
ATOM  3561 N   ILE  518     31.790  44.344   6.466  1.00 37.54      C2
ATOM  3562 H   ILE  518     32.756  44.386   6.297  1.00  0.00      C2
ATOM  3563 CA  ILE  518     30.923  43.646   5.510  1.00 36.10      C2
ATOM  3564 CB  ILE  518     31.699  42.912   4.439  1.00 34.81      C2
ATOM  3565 CG2 ILE  518     30.703  42.202   3.555  1.00 33.46      C2
ATOM  3566 CG1 ILE  518     32.623  43.842   3.699  1.00 32.91      C2
ATOM  3567 CD  ILE  518     32.019  44.700   2.596  1.00 34.09      C2
ATOM  3568 C   ILE  518     30.172  42.591   6.317  1.00 38.64      C2
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EP 0 612 846 B1

FIGURE 5


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ATOM  3569 O   HE  518      28.918  4...45   6.205  1.00 39.93      C2
ATOM  3570 N   TRP 519      30.842  41.785   7.179  1.00 38.64      C2
ATOM  3571 H   TRP 519      31.785  41.959   7.361  1.00  0.00      C2
ATOM  3572 CA  TRP 519      30.144  40.784   7.945  1.00 38.15      C2
ATOM  3573 CB  TRP 519      31.124  40.083   8.780  1.00 38.52      C2
ATOM  3574 CG  TRP 519      30.493  38.793   9.255  1.00 42.26      C2
ATOM  3575 CD2 TRP 519      29.880  38.578  10.473  1.00 41.70      C2
ATOM  3576 CE2 TRP 519      29.437  37.278  10.335  1.00 41.69      C2
ATOM  3577 CE3 TRP 519      29.648  39.282  11.629  1.00 42.26      C2
ATOM  3578 CD1 TRP 519      30.448  37.695   8.419  1.00 42.92      C2
ATOM  3579 NE1 TRP 519      29.788  36.798   9.196  1.00 44.19      C2
ATOM  3580 HE1 TRP 519      29.485  35.935   8.741  1.00  0.00      C2
ATOM  3581 CZ2 TRP 519      28.753  36.671  11.360  1.00 41.91      C2
ATOM  3582 CZ3 TRP 519      28.964  38.666  12.652  1.00 41.77      C2
ATOM  3583 CH2 TRP 519      28.522  37.375  12.515  1.00 41.05      C2
ATOM  3584 C   TRP 519      29.027  41.368   8.815  1.00 39.33      C2
ATOM  3585 O   TRP 519      27.888  40.919   8.726  1.00 38.28      C2
ATOM  3586 N   GLN 520      29.264  42.375   9.650  1.00 41.86      C2
ATOM  3587 H   GLN 520      30.180  42.717   9.700  1.00  0.00      C2
ATOM  3588 CA  GLN 520      28.240  43.016  10.464  1.00 44.63      C2
ATOM  3589 CB  GLN 520      28.691  44.198  11.239  1.00 47.03      C2
ATOM  3590 CG  GLN 520      29.602  43.808  12.360  1.00 54.78      C2
ATOM  3591 CD  GLN 520      29.910  45.009  13.243  1.00 60.14      C2
ATOM  3592 OE1 GLN 520      28.988  45.566  13.854  1.00 61.62      C2
ATOM  3593 NE2 GLN 520      31.172  45.456  13.371  1.00 60.46      C2
ATOM  3594 HE21 GLN 520      31.289  46.260  13.910  1.00  0.00      C2
ATOM  3595 HE22 GLN 520      31.895  44.966  12.932  1.00  0.00      C2
ATOM  3596 C   GLN 520      27.141  43.577   9.621  1.00 46.28      C2
ATOM  3597 O   GLN 520      26.001  43.474  10.059  1.00 48.62      C2
ATOM  3598 N   GLN 521      27.362  44.145   8.442  1.00 46.99      C2
ATOM  3599 H   GLN 521      28.272  44.257   8.092  1.00  0.00      C2
ATOM  3600 CA  GLN 521      26.226  44.638   7.716  1.00 49.02      C2
ATOM  3601 CB  GLN 521      26.632  45.553   6.566  1.00 50.06      C2
ATOM  3602 CG  GLN 521      25.456  46.226   5.790  1.00 50.87      C2
ATOM  3603 CD  GLN 521      24.616  47.278   6.534  1.00 51.82      C2
ATOM  3604 OE1 GLN 521      24.864  47.694   7.671  1.00 52.47      C2
ATOM  3605 NE2 GLN 521      23.577  47.776   5.888  1.00 50.36      C2
ATOM  3606 HE21 GLN 521      23.392  47.455   4.987  1.00  0.00      C2
ATOM  3607 HE22 GLN 521      23.044  48.424   6.390  1.00  0.00      C2
ATOM  3608 C   GLN 521      25.454  43.446   7.155  1.00 50.15      C2
ATOM  3609 O   GLN 521      24.214  43.514   7.177  1.00 51.82      C2
ATOM  3610 N   MET 522      26.057  42.348   6.668  1.00 49.18      C2
ATOM  3611 H   MET 522      27.038  42.291   6.688  1.00  0.00      C2
ATOM  3612 CA  MET 522      25.280  41.227   6.171  1.00 48.22      C2
ATOM  3613 CB  MET 522      26.185  40.167   5.607  1.00 46.36      C2
ATOM  3614 CG  MET 522      26.942  40.661   4.412  1.00 44.32      C2
ATOM  3615 SD  MET 522      27.855  39.435   3.426  1.00 48.35      C2
ATOM  3616 CE  MET 522      28.795  38.447   4.565  1.00 42.80      C2
ATOM  3617 C   MET 522      24.453  40.642   7.316  1.00 50.14      C2
ATOM  3618 O   MET 522      23.380  40.124   7.038  1.00 50.60      C2
ATOM  3619 N   GLU 523      24.848  40.722   8.596  1.00 51.91      C2
ATOM  3620 H   GLU 523      25.766  41.031   8.769  1.00  0.00      C2
ATOM  3621 CA  GLU 523      24.027  40.313   9.718  1.00 54.53      C2
ATOM  3622 CB  GLU 523      24.654  40.486  11.081  1.00 54.68      C2
ATOM  3623 CG  GLU 523      25.732  39.525  11.398  1.00 57.05      C2
ATOM  3624 CD  GLU 523      25.386  38.150  10.888  1.00 61.72      C2
ATOM  3625 OE1 GLU 523      24.515  37.487  11.477  1.00 64.66      C2
ATOM  3626 OE2 GLU 523      25.979  37.773   9.872  1.00 63.19      C2
ATOM  3627 C   GLU 523      22.773  41.116   9.836  1.00 58.29      C2
ATOM  3628 O   GLU 523      21.688  40.538   9.850  1.00 59.32      C2
ATOM  3629 N   ALA 524      22.920  42.432   9.992  1.00 60.41      C2
ATOM  3630 H   ALA 524      23.834  42.798  10.024  1.00  0.00      C2
ATOM  3631 CA  ALA 524      21.815  43.360  10.076  1.00 63.58      C2
ATOM  3632 CB  ALA 524      22.382  44.768   9.992  1.00 64.11      C2
ATOM  3633 C   ALA 524      20.818  43.109   8.946  1.00 64.79      C2
ATOM  3634 O   ALA 524      19.655  42.824   9.206  1.00 65.69      C2
ATOM  3635 N   ALA 525      21.251  43.083   7.693  1.00 66.44      C2
ATOM  3636 H   ALA 525      22.196  43.283   7.516  1.00  0.00      C2
ATOM  3637 CA  ALA 525      20.371  42.789   6.574  1.00 68.58      C2
ATOM  3638 CB  ALA 525      21.117  43.044   5.288  1.00 67.42      C2
ATOM  3639 C   ALA 525      19.841  41.356   6.558  1.00 71.11      C2
ATOM  3640 O   ALA 525      19.116  40.946   5.651  1.00 71.65      C2
ATOM  3641 N   GLY 526      20.257  40.510   7.498  1.00 74.20      C2
ATOM  3642 H   GLY 526      21.019  40.780   8.043  1.00  0.00      C2
ATOM  3643 CA  GLY 526      19.728  39.157   7.653  1.00 76.50      C2
ATOM  3644 C   GLY 526      20.430  38.085   6.842  1.00 78.19      C2
ATOM  3645 O   GLY 526      20.174  36.910   7.094  1.00 79.05      C2
ATOM  3646 N   MET 527      21.308  38.443   5.970  1.00 78.58      C2
ATOM  3647 H   MET 527      21.759  39.337   6.075  1.00  0.00      C2
ATOM  3648 CA  MET 527      22.055  37.489   5.063  1.00 81.73      C2
ATOM  3649 CB  MET 527      22.771  38.256   3.928  1.00 81.72      C2
ATOM  3650 CG  MET 527      22.185  39.719   3.740  1.00 81.52      C2
ATOM  3651 SD  MET 527      23.364  40.523   2.436  1.00 87.64      C2
ATOM  3652 CE  MET 527      22.600  42.117   2.403  1.00 84.47      C2
ATOM  3653 C   MET 527      23.078  36.584   5.780  1.00 82.64      C2
ATOM  3654 OT1 MET 527      22.974  35.357   5.624  1.00 83.38      C2
ATOM  3655 OT2 MET 527      23.949  37.104   6.500  1.00 82.99      C2
ATOM  3656 CB  MET 538      47.224  28.531   2.401  1.00 77.43      C3
ATOM  3657 CG  MET 538      47.397  30.041   2.427  1.00 77.15      C3
ATOM  3658 SD  MET 538      46.205  30.708   3.604  1.00 79.03      C3
ATOM  3659 CE  MET 538      44.850  31.067   2.515  1.00 77.20      C3
ATOM  3660 C   MET 538      48.549  27.839   0.386  1.00 75.32      C3
ATOM  3661 O   MET 538      49.130  26.745   0.405  1.00 77.11      C3
ATOM  3662 HT1 MET 538      47.563  26.068   1.449  1.00  0.00      C3
ATOM  3663 HT2 MET 538      46.638  26.204   0.075  1.00  0.00      C3
ATOM  3664 N   MET 538      46.724  26.552   1.050  1.00 77.52      C3
ATOM  3665 HT3 MET 538      45.873  26.401   1.617  1.00  0.00      C3
ATOM  3666 CA  MET 538      47.153  27.940   0.995  1.00 76.57      C3
ATOM  3667 N   PRO 539      49.089  28.870  -0.224  1.00 71.65      C3
ATOM  3668 CD  PRO 539      48.346  29.821  -1.046  1.00 72.06      C3
ATOM  3669 CA  PRO 539      50.526  29.020  -0.349  1.00 70.14      C3
ATOM  3670 CB  PRO 539      50.677  30.465  -1.006  1.00 71.09      C3
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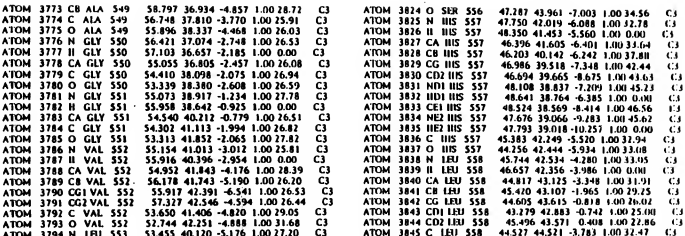
FIGURE 5

FIGURE 5



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ATOM  3773 CB  ALA  549      58.797  36.934  -4.857  1.00 28.72      C3
ATOM  3774 C   ALA  549      56.748  37.810  -3.770  1.00 25.91      C3
ATOM  3775 O   ALA  549      55.896  38.337  -4.468  1.00 26.03      C3
ATOM  3776 N   GLY  550      56.421  37.074  -2.748  1.00 26.53      C3
ATOM  3777 H   GLY  550      57.103  36.657  -2.185  1.00  0.00      C3
ATOM  3778 CA  GLY  550      55.055  36.805  -2.457  1.00 26.08      C3
ATOM  3779 C   GLY  550      54.410  38.098  -2.075  1.00 26.94      C3
ATOM  3780 O   GLY  550      53.339  38.380  -2.608  1.00 26.59      C3
ATOM  3781 N   GLY  551      55.073  38.917  -1.234  1.00 27.78      C3
ATOM  3782 H   GLY  551      55.958  38.642  -0.925  1.00  0.00      C3
ATOM  3783 CA  GLY  551      54.540  40.212  -0.779  1.00 26.51      C3
ATOM  3784 C   GLY  551      54.302  41.112  -1.994  1.00 26.82      C3
ATOM  3785 O   GLY  551      53.313  41.852  -2.065  1.00 27.82      C3
ATOM  3786 N   VAL  552      55.154  41.013  -3.012  1.00 25.81      C3
ATOM  3787 H   VAL  552      55.916  40.396  -2.954  1.00  0.00      C3
ATOM  3788 CA  VAL  552      54.952  41.843  -4.176  1.00 28.39      C3
ATOM  3789 CB  VAL  552      56.178  41.743  -5.190  1.00 26.20      C3
ATOM  3790 CG1 VAL  552      55.917  42.391  -6.541  1.00 26.53      C3
ATOM  3791 CG2 VAL  552      57.327  42.546  -4.594  1.00 26.44      C3
ATOM  3792 C   VAL  552      53.650  41.406  -4.820  1.00 29.05      C3
ATOM  3793 O   VAL  552      52.744  42.251  -4.888  1.00 31.68      C3
ATOM  3794 N   LEU  553      53.455  40.120  -5.176  1.00 27.20      C3
ATOM  3795 H   LEU  553      54.122  39.447  -4.908  1.00  0.00      C3
ATOM  3796 CA  LEU  553      52.266  39.705  -5.915  1.00 25.08      C3
ATOM  3797 CB  LEU  553      52.357  38.262  -6.363  1.00 24.86      C3
ATOM  3798 CG  LEU  553      53.432  37.955  -7.357  1.00 23.06      C3
ATOM  3799 CD1 LEU  553      54.073  36.623  -7.092  1.00 24.52      C3
ATOM  3800 CD2 LEU  553      52.794  38.061  -8.703  1.00 21.87      C3
ATOM  3801 C   LEU  553      51.012  39.825  -5.114  1.00 23.72      C3
ATOM  3802 O   LEU  553      49.982  40.138  -5.712  1.00 24.63      C3
ATOM  3803 N   VAL  554      50.962  39.580  -3.803  1.00 24.37      C3
ATOM  3804 H   VAL  554      51.774  39.350  -3.295  1.00  0.00      C3
ATOM  3805 CA  VAL  554      49.660  39.691  -3.180  1.00 26.36      C3
ATOM  3806 CB  VAL  554      49.472  38.751  -1.802  1.00 26.55      C3
ATOM  3807 CG1 VAL  554      50.696  37.933  -1.418  1.00 23.95      C3
ATOM  3808 CG2 VAL  554      48.953  39.614  -0.682  1.00 25.58      C3
ATOM  3809 C   VAL  554      49.322  41.175  -2.960  1.00 27.53      C3
ATOM  3810 O   VAL  554      48.142  41.502  -3.192  1.00 27.44      C3
ATOM  3811 N   ALA  555      50.277  42.106  -2.716  1.00 28.04      C3
ATOM  3812 H   ALA  555      51.221  41.831  -2.658  1.00  0.00      C3
ATOM  3813 CA  ALA  555      49.956  43.539  -2.509  1.00 28.57      C3
ATOM  3814 CB  ALA  555      51.161  44.427  -2.217  1.00 28.07      C3
ATOM  3815 C   ALA  555      49.407  44.055  -3.803  1.00 28.12      C3
ATOM  3816 O   ALA  555      48.425  44.803  -3.847  1.00 30.12      C3
ATOM  3817 N   SER  556      49.985  43.521  -4.839  1.00 26.44      C3
ATOM  3818 H   SER  556      50.781  42.956  -4.710  1.00  0.00      C3
ATOM  3819 CA  SER  556      49.548  43.810  -6.152  1.00 30.09      C3
ATOM  3820 CB  SER  556      50.684  43.277  -6.965  1.00 31.42      C3
ATOM  3821 OG  SER  556      50.442  43.338  -8.344  1.00 37.88      C3
ATOM  3822 HG  SER  556      49.966  44.144  -8.576  1.00  0.00      C3
ATOM  3823 C   SER  556      48.143  43.243  -6.454  1.00 32.78      C3
ATOM  3824 O   SER  556      47.287  43.961  -7.003  1.00 34.56      C3
ATOM  3825 N   HIS  557      47.750  42.019  -6.088  1.00 32.78      C3
ATOM  3826 H   HIS  557      48.350  41.453  -5.560  1.00  0.00      C3
ATOM  3827 CA  HIS  557      46.396  41.605  -6.401  1.00 33.64      C3
ATOM  3828 CB  HIS  557      46.203  40.142  -6.242  1.00 37.88      C3
ATOM  3829 CG  HIS  557      46.986  39.518  -7.348  1.00 42.44      C3
ATOM  3830 CD2 HIS  557      46.694  39.665  -8.675  1.00 43.63      C3
ATOM  3831 ND1 HIS  557      48.108  38.837  -7.209  1.00 45.23      C3
ATOM  3832 HD1 HIS  557      48.641  38.764  -6.385  1.00  0.00      C3
ATOM  3833 CE1 HIS  557      48.524  38.569  -8.414  1.00 46.56      C3
ATOM  3834 NE2 HIS  557      47.676  39.066  -9.283  1.00 45.62      C3
ATOM  3835 HE2 HIS  557      47.793  39.018 -10.257  1.00  0.00      C3
ATOM  3836 C   HIS  557      45.383  42.249  -5.520  1.00 32.94      C3
ATOM  3837 O   HIS  557      44.256  42.444  -5.934  1.00 33.08      C3
ATOM  3838 N   LEU  558      45.744  42.534  -4.280  1.00 33.05      C3
ATOM  3839 H   LEU  558      46.657  42.356  -3.986  1.00  0.00      C3
ATOM  3840 CA  LEU  558      44.817  43.125  -3.348  1.00 31.91      C3
ATOM  3841 CB  LEU  558      45.420  43.107  -1.965  1.00 29.25      C3
ATOM  3842 CG  LEU  558      44.605  43.615  -0.818  1.00 26.02      C3
ATOM  3843 CD1 LEU  558      43.279  42.883  -0.742  1.00 25.00      C3
ATOM  3844 CD2 LEU  558      45.496  43.571  0.408  1.00 22.86      C3
ATOM  3845 C   LEU  558      44.527  44.521  -3.783  1.00 32.47      C3
ATOM  3846 O   LEU  558      43.402  44.944  -3.596  1.00 33.97      C3
ATOM  3847 N   GLN  559      45.482  45.231  -4.370  1.00 34.36      C3
ATOM  3848 H   GLN  559      46.386  44.855  -4.406  1.00  0.00      C3
ATOM  3849 CA  GLN  559      45.255  46.569  -4.912  1.00 36.75      C3
ATOM  3850 CB  GLN  559      46.598  47.067  -5.470  1.00 39.63      C3
ATOM  3851 CG  GLN  559      46.707  48.543  -5.875  1.00 42.07      C3
ATOM  3852 CD  GLN  559      46.530  49.618  -4.793  1.00 41.53      C3
ATOM  3853 OE1 GLN  559      45.961  50.687  -5.057  1.00 41.25      C3
ATOM  3854 NE2 GLN  559      46.951  49.416  -3.561  1.00 37.96      C3
ATOM  3855 HE21 GLN  559      47.271  48.528  -3.311  1.00  0.00      C3
ATOM  3856 HE22 GLN  559      47.001  50.190  -2.967  1.00  0.00      C3
ATOM  3857 C   GLN  559      44.142  46.635  -5.976  1.00 35.22      C3
ATOM  3858 O   GLN  559      43.165  47.404  -5.839  1.00 34.93      C3
ATOM  3859 N   SER  560      44.260  45.817  -7.025  1.00 33.46      C3
ATOM  3860 H   SER  560      45.083  45.292  -7.154  1.00  0.00      C3
ATOM  3861 CA  SER  560      43.222  45.683  -8.049  1.00 32.88      C3
ATOM  3862 CB  SER  560      43.693  44.776  -9.088  1.00 34.05      C3
ATOM  3863 OG  SER  560      45.021  45.174  -9.281  1.00 42.40      C3
ATOM  3864 HG  SER  560      45.042  45.996  -9.783  1.00  0.00      C3
ATOM  3865 C   SER  560      41.885  45.133  -7.559  1.00 32.01      C3
ATOM  3866 O   SER  560      40.791  45.582  -7.920  1.00 32.23      C3
ATOM  3867 N   PHE  561      41.969  44.123  -6.710  1.00 29.50      C3
ATOM  3868 H   PHE  561      42.850  43.767  -6.464  1.00  0.00      C3
ATOM  3869 CA  PHE  561      40.803  43.529  -6.118  1.00 32.88      C3
ATOM  3870 CB  PHE  561      41.237  42.541  -5.040  1.00 26.27      C3
ATOM  3871 CG  PHE  561      40.069  41.966  -4.268  1.00 25.68      C3
ATOM  3872 CD1 PHE  561      39.282  40.999  -4.846  1.00 25.44      C3
ATOM  3873 CD2 PHE  561      39.761  42.482  -3.051  1.00 25.45      C3
ATOM  3874 CE1 PHE  561      38.166  40.551  -4.215  1.00 21.49      C3
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FIGURE 5

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ATOM  3875 CE2 PHE  561      38.635  -2.027  -2.421  1.00 26.89      C3
ATOM  3876 CZ  PHE  561      37.853  41.074  -3.008  1.00 24.29      C3
ATOM  3877 C   PHE  561      39.987  44.645  -5.505  1.00 28.81      C3
ATOM  3878 O   PHE  561      38.789  44.697  -5.731  1.00 29.31      C3
ATOM  3879 N   LEU  562      40.672  45.565  -4.797  1.00 28.39      C3
ATOM  3880 H   LEU  562      41.643  45.462  -4.707  1.00 0.00       C3
ATOM  3881 CA  LEU  562      40.033  46.617  -4.057  1.00 26.51      C3
ATOM  3882 CB  LEU  562      40.964  47.203  -3.074  1.00 23.80      C3
ATOM  3883 CG  LEU  562      41.047  46.411  -1.816  1.00 24.85      C3
ATOM  3884 CD1 LEU  562      42.207  46.868  -1.049  1.00 24.07      C3
ATOM  3885 CD2 LEU  562      39.794  46.551  -1.008  1.00 25.13      C3
ATOM  3886 C   LEU  562      39.586  47.669  -4.988  1.00 29.27      C3
ATOM  3887 O   LEU  562      38.580  48.304  -4.681  1.00 29.83      C3
ATOM  3888 N   GLU  563      40.239  47.871  -6.115  1.00 30.88      C3
ATOM  3889 H   GLU  563      41.052  47.368  -6.325  1.00 0.00       C3
ATOM  3890 CA  GLU  563      39.738  48.908  -6.966  1.00 36.88      C3
ATOM  3891 CB  GLU  563      40.660  49.142  -8.137  1.00 40.80      C3
ATOM  3892 CG  GLU  563      41.999  49.628  -7.682  1.00 48.55      C3
ATOM  3893 CD  GLU  563      43.148  49.277  -8.619  1.00 55.42      C3
ATOM  3894 OE1 GLU  563      44.301  49.283  -8.135  1.00 57.39      C3
ATOM  3895 OE2 GLU  563      42.886  48.986  -9.808  1.00 56.44      C3
ATOM  3896 C   GLU  563      38.375  48.469  -7.466  1.00 39.02      C3
ATOM  3897 O   GLU  563      37.388  49.170  -7.270  1.00 39.09      C3
ATOM  3898 N   VAL  564      38.289  47.255  -8.030  1.00 42.30      C3
ATOM  3899 H   VAL  564      39.107  46.714  -8.063  1.00 0.00       C3
ATOM  3900 CA  VAL  564      37.052  46.683  -8.558  1.00 41.84      C3
ATOM  3901 CB  VAL  564      37.333  45.255  -9.041  1.00 42.27      C3
ATOM  3902 CG1 VAL  564      36.055  44.538  -9.435  1.00 41.17      C3
ATOM  3903 CG2 VAL  564      38.283  45.348 -10.241  1.00 43.11      C3
ATOM  3904 C   VAL  564      36.030  46.709  -7.442  1.00 41.68      C3
ATOM  3905 O   VAL  564      34.892  47.015  -7.697  1.00 42.34      C3
ATOM  3906 N   SER  565      36.419  46.501  -6.206  1.00 42.39      C3
ATOM  3907 H   SER  565      37.333  46.173  -6.063  1.00 0.00       C3
ATOM  3908 CA  SER  565      35.562  46.602  -5.064  1.00 44.85      C3
ATOM  3909 CB  SER  565      36.344  46.013  -3.894  1.00 46.54      C3
ATOM  3910 OG  SER  565      35.590  45.714  -2.731  1.00 51.75      C3
ATOM  3911 HG  SER  565      35.060  46.481  -2.491  1.00 0.00       C3
ATOM  3912 C   SER  565      35.167  48.063  -4.871  1.00 45.70      C3
ATOM  3913 O   SER  565      34.038  48.287  -4.446  1.00 46.87      C3
ATOM  3914 N   TYR  566      35.965  49.093  -5.146  1.00 47.59      C3
ATOM  3915 H   TYR  566      36.893  48.908  -5.386  1.00 0.00       C3
ATOM  3916 CA  TYR  566      35.518  50.474  -5.086  1.00 49.68      C3
ATOM  3917 CB  TYR  566      36.765  51.362  -5.164  1.00 56.17      C3
ATOM  3918 CG  TYR  566      36.715  52.632  -6.007  1.00 64.64      C3
ATOM  3919 CD1 TYR  566      37.264  52.538  -7.278  1.00 69.53      C3
ATOM  3920 CE1 TYR  566      37.212  53.613  -8.151  1.00 73.71      C3
ATOM  3921 CD2 TYR  566      36.109  53.797  -5.569  1.00 67.98      C3
ATOM  3922 CE2 TYR  566      36.048  54.888  -6.441  1.00 72.92      C3
ATOM  3923 CZ  TYR  566      36.599  54.787  -7.735  1.00 75.29      C3
ATOM  3924 OH  TYR  566      36.538  55.838  -8.652  1.00 77.42      C3
ATOM  3925 HH  TYR  566      36.905  55.565  -9.494  1.00 0.00       C3

ATOM  3926 C   TYR  566      34.524  50.696  -6.217  1.00 48.48      C3
ATOM  3927 O   TYR  566      33.545  51.376  -5.950  1.00 46.15      C3
ATOM  3928 N   ALA  567      34.679  50.115  -7.417  1.00 49.14      C3
ATOM  3929 H   ALA  567      35.512  49.625  -7.572  1.00 0.00       C3
ATOM  3930 CA  ALA  567      33.670  50.165  -8.490  1.00 52.09      C3
ATOM  3931 CB  ALA  567      34.210  49.574  -9.788  1.00 48.37      C3
ATOM  3932 C   ALA  567      32.315  49.449  -8.238  1.00 55.31      C3
ATOM  3933 O   ALA  567      31.226  50.008  -8.501  1.00 56.87      C3
ATOM  3934 N   VAL  568      32.247  48.211  -7.736  1.00 57.66      C3
ATOM  3935 H   VAL  568      33.083  47.729  -7.564  1.00 0.00       C3
ATOM  3936 CA  VAL  568      30.980  47.573  -7.490  1.00 59.61      C3
ATOM  3937 CB  VAL  568      31.119  46.031  -7.339  1.00 58.65      C3
ATOM  3938 CG1 VAL  568      31.239  45.508  -5.911  1.00 60.27      C3
ATOM  3939 CG2 VAL  568      29.851  45.471  -7.922  1.00 60.44      C3
ATOM  3940 C   VAL  568      30.393  48.177  -6.245  1.00 62.66      C3
ATOM  3941 O   VAL  568      29.174  48.154  -6.180  1.00 64.78      C3
ATOM  3942 N   LEU  569      31.075  48.737  -5.248  1.00 66.15      C3
ATOM  3943 H   LEU  569      32.058  48.719  -5.243  1.00 0.00       C3
ATOM  3944 CA  LEU  569      30.359  49.334  -4.123  1.00 69.85      C3
ATOM  3945 CB  LEU  569      31.285  49.858  -3.023  1.00 69.91      C3
ATOM  3946 CG  LEU  569      32.007  48.887  -2.095  1.00 70.17      C3
ATOM  3947 CD1 LEU  569      32.847  49.687  -1.140  1.00 70.19      C3
ATOM  3948 CD2 LEU  569      31.039  48.054  -1.286  1.00 70.56      C3
ATOM  3949 C   LEU  569      29.567  50.509  -4.667  1.00 72.09      C3
ATOM  3950 O   LEU  569      28.365  50.553  -4.425  1.00 73.80      C3
ATOM  3951 N   ARG  570      30.180  51.391  -5.479  1.00 75.95      C3
ATOM  3952 H   ARG  570      31.153  51.299  -5.580  1.00 0.00       C3
ATOM  3953 CA  ARG  570      29.510  52.498  -6.173  1.00 78.78      C3
ATOM  3954 CB  ARG  570      30.399  53.068  -7.308  1.00 80.07      C3
ATOM  3955 CG  ARG  570      29.658  54.222  -7.997  1.00 84.16      C3
ATOM  3956 CD  ARG  570      29.976  54.744  -9.417  1.00 85.66      C3
ATOM  3957 NE  ARG  570      28.892  55.690  -9.737  1.00 85.67      C3
ATOM  3958 HE  ARG  570      27.971  55.354  -9.727  1.00 0.00       C3
ATOM  3959 CZ  ARG  570      29.051  56.991 -10.026  1.00 85.06      C3
ATOM  3960 NH1 ARG  570      30.240  57.590 -10.082  1.00 84.43      C3
ATOM  3961 1HH1 ARG  570      31.069  57.056 -9.908  1.00 0.00       C3
ATOM  3962 2HH1 ARG  570      30.295  58.561 -10.314  1.00 0.00       C3
ATOM  3963 NH2 ARG  570      27.958  57.736 -10.154  1.00 84.57      C3
ATOM  3964 1HH2 ARG  570      27.059  57.316 -10.040  1.00 0.00       C3
ATOM  3965 2HH2 ARG  570      28.042  58.708 -10.375  1.00 0.00       C3
ATOM  3966 C   ARG  570      28.201  52.009  -6.812  1.00 79.92      C3
ATOM  3967 O   ARG  570      27.107  52.565  -6.709  1.00 79.61      C3
ATOM  3968 N   HIS  571      28.362  50.900  -7.511  1.00 81.35      C3
ATOM  3969 H   HIS  571      29.214  50.417  -7.440  1.00 0.00       C3
ATOM  3970 CA  HIS  571      27.247  50.306  -8.197  1.00 82.75      C3
ATOM  3971 C8  HIS  571      27.882  49.274  -9.167  1.00 83.42      C3
ATOM  3972 CG  HIS  571      28.633  50.029 -10.280  1.00 85.08      C3
ATOM  3973 CD2 HIS  571      28.921  49.579 -11.532  1.00 85.81      C3
ATOM  3974 ND1 HIS  571      29.074  51.303 -10.268  1.00 86.25      C3
ATOM  3975 HD1 HIS  571      29.080  51.900  -9.489  1.00 0.00       C3
ATOM  3976 CE1 HIS  571      29.595  51.595 -11.439  1.00 86.01      C3
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FIGURE 5


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ATOM  3977 NE2 HIS  571      29.494  50.518 -12.187  1.00 86.28      C3
ATOM  3978 HE2 HIS  571      29.801  50.468 -13.119  1.00  0.00      C3
ATOM  3979 C   HIS  571      26.225  49.759  -7.195  1.00 83.31      C3
ATOM  3980 O   HIS  571      25.075  50.194  -7.301  1.00 84.06      C3
ATOM  3981 N   LEU  572      26.540  48.963  -6.158  1.00 83.11      C3
ATOM  3982 H   LEU  572      27.474  48.824  -5.915  1.00  0.00      C3
ATOM  3983 CA  LEU  572      25.527  48.457  -5.241  1.00 83.71      C3
ATOM  3984 CB  LEU  572      26.085  47.267  -4.454  1.00 83.57      C3
ATOM  3985 CG  LEU  572      25.439  45.884  -4.721  1.00 83.79      C3
ATOM  3986 CD1 LEU  572      25.783  45.386  -6.127  1.00 84.16      C3
ATOM  3987 CD2 LEU  572      25.958  44.866  -3.714  1.00 84.08      C3
ATOM  3988 C   LEU  572      24.997  49.511  -4.261  1.00 84.78      C3
ATOM  3989 O   LEU  572      24.265  49.192  -3.295  1.00 84.85      C3
ATOM  3990 N   ALA  573      25.349  50.796  -4.483  1.00 85.56      C3
ATOM  3991 H   ALA  573      26.020  50.980  -5.174  1.00  0.00      C3
ATOM  3992 CA  ALA  573      24.822  51.925  -3.721  1.00 85.90      C3
ATOM  3993 CB  ALA  573      25.600  53.207  -3.970  1.00 85.79      C3
ATOM  3994 C   ALA  573      23.373  52.245  -4.057  1.00 87.21      C3
ATOM  3995 OT1 ALA  573      22.610  52.413  -3.099  1.00 88.33      C3
ATOM  3996 OT2 ALA  573      23.022  52.309  -5.248  1.00 88.34      C3
ATOM  3997 OH2 H2O  603      26.735  24.280   5.161  1.00 27.27      W
ATOM  3998 H1  H2O  603      27.332  24.335   4.407  1.00  0.00      W
ATOM  3999 H2  H2O  603      26.288  23.435   4.992  1.00  0.00      W
ATOM  4000 OH2 H2O  605      47.880  37.960  12.073  1.00 56.30      W
ATOM  4001 H1  H2O  605      47.789  37.874  13.031  1.00  0.00      W
ATOM  4002 H2  H2O  605      46.980  37.858  11.753  1.00  0.00      W
ATOM  4003 OH2 H2O  607      40.001  49.224   7.214  1.00 40.04      W
ATOM  4004 H1  H2O  607      40.471  48.761   7.909  1.00  0.00      W
ATOM  4005 H2  H2O  607      40.123  48.642   6.457  1.00  0.00      W
ATOM  4006 OH2 H2O  610      59.883  42.530  -9.698  1.00 38.90      W
ATOM  4007 H1  H2O  610      60.512  41.833  -9.477  1.00  0.00      W
ATOM  4008 H2  H2O  610      59.189  42.046 -10.160  1.00  0.00      W
ATOM  4009 OH2 H2O  611      57.178  35.940 -14.220  1.00 34.63      W
ATOM  4010 H1  H2O  611      57.174  36.545 -14.974  1.00  0.00      W
ATOM  4011 H2  H2O  611      57.989  36.211 -13.757  1.00  0.00      W
ATOM  4012 OH2 H2O  612      25.793  27.337  19.130  1.00 29.21      W
ATOM  4013 H1  H2O  612      26.709  27.661  19.145  1.00  0.00      W
ATOM  4014 H2  H2O  612      25.762  26.792  19.929  1.00  0.00      W
ATOM  4015 OH2 H2O  615      29.766  34.284   9.444  1.00 45.03      W
ATOM  4016 H1  H2O  615      30.017  34.618  10.308  1.00  0.00      W
ATOM  4017 H2  H2O  615      29.113  33.592   9.660  1.00  0.00      W
ATOM  4018 OH2 H2O  617      37.316  40.012  10.872  1.00 35.21      W
ATOM  4019 H1  H2O  617      36.600  40.017  11.519  1.00  0.00      W
ATOM  4020 H2  H2O  617      37.944  39.376  11.259  1.00  0.00      W
ATOM  4021 OH2 H2O  619      40.370  52.041  -7.387  1.00 29.62      W
ATOM  4022 H1  H2O  619      40.672  52.724  -6.779  1.00  0.00      W
ATOM  4023 H2  H2O  619      39.505  51.810  -7.052  1.00  0.00      W
ATOM  4024 OH2 H2O  621      27.903  32.440  10.664  1.00 39.99      W
ATOM  4025 H1  H2O  621      27.553  33.207  11.141  1.00  0.00      W
ATOM  4026 H2  H2O  621      27.929  31.808  11.398  1.00  0.00      W
ATOM  4027 OH2 H2O  622      25.057  31.972  13.675  1.00 32.70      W
ATOM  4028 H1  H2O  622      24.393  32.417  14.215  1.00  0.00      W
ATOM  4029 H2  H2O  622      24.469  31.428  13.112  1.00  0.00      W
ATOM  4030 OH2 H2O  623      20.791  28.583  14.218  1.00 50.17      W
ATOM  4031 H1  H2O  623      20.499  28.803  13.325  1.00  0.00      W
ATOM  4032 H2  H2O  623      19.939  28.549  14.688  1.00  0.00      W
ATOM  4033 OH2 H2O  625      22.680  78.881   2.761  1.00 40.48      W
ATOM  4034 H1  H2O  625      21.938  78.856   3.375  1.00  0.00      W
ATOM  4035 H2  H2O  625      22.266  79.246   1.970  1.00  0.00      W
ATOM  4036 OH2 H2O  626      39.689  36.486   9.710  1.00 23.16      W
ATOM  4037 H1  H2O  626      39.090  35.724   9.672  1.00  0.00      W
ATOM  4038 H2  H2O  626      39.627  36.872   8.853  1.00  0.00      W
ATOM  4039 OH2 H2O  627      42.035  78.320   5.607  1.00 46.19      W
ATOM  4040 H1  H2O  627      42.416  77.450   5.832  1.00  0.00      W
ATOM  4041 H2  H2O  627      41.243  78.146   5.181  1.00  0.00      W
ATOM  4042 OH2 H2O  631      47.227  31.440   6.299  1.00 34.17      W
ATOM  4043 H1  H2O  631      47.533  32.209   5.809  1.00  0.00      W
ATOM  4044 H2  H2O  631      47.442  30.713   5.714  1.00  0.00      W
ATOM  4045 OH2 H2O  636      24.043  65.423  -0.336  1.00 73.38      W
ATOM  4046 H1  H2O  636      24.179  65.781  -1.228  1.00  0.00      W
ATOM  4047 H2  H2O  636      23.469  66.096   0.054  1.00  0.00      W
ATOM  4048 OH2 H2O  638      38.984  -0.955 -11.226  1.00 70.97      W
ATOM  4049 H1  H2O  638      38.283  67.402 -11.580  1.00  0.00      W
ATOM  4050 H2  H2O  638      39.568  68.046 -11.998  1.00  0.00      W
ATOM  4051 OH2 H2O  639      27.910  66.675  -7.733  1.00 48.40      W
ATOM  4052 H1  H2O  639      28.192  67.028  -6.876  1.00  0.00      W
ATOM  4053 H2  H2O  639      26.975  66.791  -7.705  1.00  0.00      W
ATOM  4054 OH2 H2O  643      50.619  62.802   0.813  1.00 36.55      W
ATOM  4055 H1  H2O  643      51.579  62.904   0.824  1.00  0.00      W
ATOM  4056 H2  H2O  643      50.301  63.665   0.525  1.00  0.00      W
ATOM  4057 OH2 H2O  646      62.897  38.367   3.759  1.00 73.55      W
ATOM  4058 H1  H2O  646      62.414  38.098   2.978  1.00  0.00      W
ATOM  4059 H2  H2O  646      62.244  38.247   4.461  1.00  0.00      W
ATOM  4060 OH2 H2O  650      29.587  68.480  -9.555  1.00 65.67      W
ATOM  4061 H1  H2O  650      28.846  68.630 -10.148  1.00  0.00      W
ATOM  4062 H2  H2O  650      29.180  67.844  -8.936  1.00  0.00      W
ATOM  4063 OH2 H2O  652      51.408  56.331  -4.056  1.00 62.90      W
ATOM  4064 H1  H2O  652      50.718  56.353   3.365  1.00  0.00      W
ATOM  4065 H2  H2O  652      51.052  55.671   4.648  1.00  0.00      W
ATOM  4066 OH2 H2O  653      49.404  56.022   2.161  1.00 51.28      W
ATOM  4067 H1  H2O  653      49.442  55.351   1.474  1.00  0.00      W
ATOM  4068 H2  H2O  653      49.323  56.829   1.630  1.00  0.00      W
ATOM  4069 OH2 H2O  654      68.215  42.294  -2.563  1.00 40.77      W
ATOM  4070 H1  H2O  654      68.347  41.745  -1.777  1.00  0.00      W
ATOM  4071 H2  H2O  654      68.189  43.181  -2.190  1.00  0.00      W
ATOM  4072 OH2 H2O  655      66.374  40.425  -2.489  1.00 42.31      W
ATOM  4073 H1  H2O  655      66.936  41.162  -2.766  1.00  0.00      W
ATOM  4074 H2  H2O  655      66.452  39.841  -3.252  1.00  0.00      W
ATOM  4075 OH2 H2O  656      66.927  41.428  -5.011  1.00 44.08      W
ATOM  4076 H1  H2O  656      66.207  42.071  -4.989  1.00  0.00      W
ATOM  4077 H2  H2O  656      67.542  41.824  -4.574  1.00  0.00      W
ATOM  4078 OH2 H2O  657      40.371  57.111   5.730  1.00 66.55      W
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FIGURE 5

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ATOM  4079 H1  H2O  657      39.958  ...259   5.613  1.00  0.00      W
ATOM  4080 H2  H2O  657      40.021  57.651   5.014  1.00  0.00      W
ATOM  4081 OH2 H2O  658      48.780  47.580  -3.122  1.00 52.09      W
ATOM  4082 H1  H2O  658      48.811  46.671  -3.438  1.00  0.00      W
ATOM  4083 H2  H2O  658      49.568  47.955  -3.542  1.00  0.00      W
ATOM  4084 OH2 H2O  663      29.095  62.889   1.825  1.00 39.23      W
ATOM  4085 H1  H2O  663      29.380  62.827   2.739  1.00  0.00      W
ATOM  4086 H2  H2O  663      28.377  63.526   1.887  1.00  0.00      W
ATOM  4087 OH2 H2O  664      27.132  25.640   7.430  1.00 50.65      W
ATOM  4088 H1  H2O  664      26.870  24.838   7.876  1.00  0.00      W
ATOM  4089 H2  H2O  664      27.001  25.362   6.496  1.00  0.00      W
ATOM  4090 OH2 H2O  665      23.367  30.554  12.167  1.00 49.69      W
ATOM  4091 H1  H2O  665      24.026  30.006  11.707  1.00  0.00      W
ATOM  4092 H2  H2O  665      22.941  31.016  11.438  1.00  0.00      W
ATOM  4093 OH2 H2O  666      46.015  32.192  10.179  1.00 66.86      W
ATOM  4094 H1  H2O  666      46.060  31.519   9.497  1.00  0.00      W
ATOM  4095 H2  H2O  666      45.411  31.827  10.833  1.00  0.00      W
ATOM  4096 OH2 H2O  667      38.943  37.883  11.978  1.00 47.87      W
ATOM  4097 H1  H2O  667      39.367  37.487  11.188  1.00  0.00      W
ATOM  4098 H2  H2O  667      38.521  37.114  12.362  1.00  0.00      W
ATOM  4099 OH2 H2O  671      33.437  58.101   2.269  1.00 46.65      W
ATOM  4100 H1  H2O  671      33.555  57.162   2.433  1.00  0.00      W
ATOM  4101 H2  H2O  671      33.962  58.514   2.961  1.00  0.00      W
ATOM  4102 OH2 H2O  672      27.551  31.314  20.022  1.00 30.15      W
ATOM  4103 H1  H2O  672      27.929  32.042  20.533  1.00  0.00      W
ATOM  4104 H2  H2O  672      26.845  31.764  19.552  1.00  0.00      W
ATOM  4105 OH2 H2O  673      25.714  36.908  21.385  1.00 36.95      W
ATOM  4106 H1  H2O  673      24.806  37.123  21.637  1.00  0.00      W
ATOM  4107 H2  H2O  673      25.599  36.284  20.654  1.00  0.00      W
ATOM  4108 OH2 H2O  674      38.244  66.897  12.076  1.00 57.36      W
ATOM  4109 H1  H2O  674      37.773  67.536  12.626  1.00  0.00      W
ATOM  4110 H2  H2O  674      38.153  66.104  12.618  1.00  0.00      W
ATOM  4111 OH2 H2O  675      35.762  36.553  -3.986  1.00 58.40      W
ATOM  4112 H1  H2O  675      35.600  37.449  -3.677  1.00  0.00      W
ATOM  4113 H2  H2O  675      35.549  36.642  -4.923  1.00  0.00      W
ATOM  4114 OH2 H2O  676      30.689  32.814  25.675  1.00 59.30      W
ATOM  4115 H1  H2O  676      30.093  33.571  25.680  1.00  0.00      W
ATOM  4116 H2  H2O  676      31.550  33.214  25.540  1.00  0.00      W
END
```


EP 0 612 846 B1

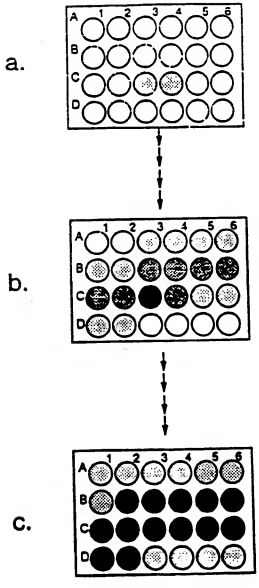

FIGURE 6